Infectious Diseases, Livestock Production and Changing Public Health Policy in Southeast Asia

A DISSERTATION SUBMITTED TO THE FACULTY OF UNIVERSITY OF MINNESOTA BY

Megan Elizabeth Peck

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Bruce H. Alexander, Ph.D., Advisor

Jeff Bender, DVM, MS, Advisor

July 2017

Acknowledgements

First I want to express my sincere gratitude and deep appreciation for my advisors, Dr. Bruce Alexander and Dr. Jeff Bender. Your thoughtful mentorship was always there to support me throughout my PhD. Thank you both for your continuous optimism, guidance, patience and flexibility. I greatly admire and appreciate your spirit of adventure regarding research and your compassionate concern for public health. You both challenged me to take risks and each of you offered a model for effective approaches to addressing global health challenges. Your influence will forever shape my career. I would also like to thank all the members of my dissertation committee for your thoughtful questions, helpful comments and direction on my research.

Thank you to all the international partners and collaborators without whom this research would not be possible. A sincere thank you to Dr. Alongkorn Amonsin for the opportunity to work with you and your research team at Chulalongkorn University. Thank you to the Thailand Department of Livestock Development and particularly Dr. Chayanee Jenpanich and Karoon Chanachai for your enthusiasm and dedication to this project. I am grateful for all the farmers and their families who participated in the brucellosis research. Spending time in the field and experiencing the hospitality and graciousness of Thai farmers was particularly rewarding. A special thank you to everyone involved in the antimicrobial resistance project from the Food and Agriculture Organization of the United Nations, especially Dr. Wantanee Kalpravidh, Dr. Carolyn Benigno and Dr. Katinka de Balogh not only for this opportunity but also for your

invaluable support on this project.

My fellow graduate students Kara Gavin and Bozena Morawski, I am grateful for your never-ending moral support, knowledge sharing and much needed encouragement throughout graduate school. Thank you to all the those who provided behind the scenes support including Khosi Nkosi, Karen Brademeyer, and Debb Grove.

I would also like to express my appreciation for all the professors from the University of Minnesota School of Public Health who inspired my passion for public health and challenged me to believe we can make the world a better place. I am honored to have been a part of such a wonderful program.

I would like to acknowledge with gratitude my parents Beth and Gil, for their never-ending support, meaningful encouragement and belief in my abilities. A special note of thanks to my husband Spencer. I am deeply grateful for your enduring love, encouragement and the sacrifices you made moving to another country for me to pursue my research.

Abstract

This dissertation concentrates on two emerging trends influenced by national policies that pose potential public health and occupational risks for those involved in animal food production. These trends include the increased use of antimicrobials and its impact on antimicrobial resistance (AMR) and agricultural policies to increase animal production and the re-emergence of a zoonotic disease, brucellosis. Overall the goal of this dissertation is to characterize and better understand the interaction between agricultural policy, animal husbandry practices, occupational risks and public health. Studies in this dissertation provide information on the re-emergence of a zoonotic disease and current and proposed policy frameworks to manage and protect public health from AMR. Diseases that are transmissible either directly or indirectly between animals and humans, such as AMR and brucellosis, pose significant threats to global animal and human health. As countries continue to adapt policy to increase food production, the spread and growth of disease needs to be considered. Findings from this research can be used to inform further studies on the impact of agriculture policies and infectious diseases in low resource settings, strengthen future policy, inform future training and education initiatives and provide greater awareness and understanding of factors influencing emergence and re-emergence of infectious diseases.

Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction and background

Intensifying animal production and public health

Policy influences occupational health risks for those involved in animal food production. The nature of these risks is changing as practices in animal food production shift and expand globally (Tomley & Shirley, 2009; Thornton, 2010; Otte et al., 2007; Richter et al., 2015). Risk is particularly high among those involved in agriculture in low- and middle-income countries where there are close human-livestock interactions and regulation and enforcements are often limited (FAO, 2017; Weiss et al., 2004; Graham et al., 2008). Responses to occupational health risks among agricultural workers differ fundamentally across countries. For many countries, governments create agricultural policies to address various objectives including poverty reduction, agricultural development and addressing food security issues (Brooks, 2010; Delgado et al., 1999). Often these policies have unintentional consequences on human and animal health (Morse, 2001; Fresco, 2009; Jones et al., 2008; Perry et al., 2008). This research focuses on understanding the consequences of the expansion and intensification of food animal production and on the role of policy in how countries are responding and adapting to these changes.

AMR poses a significant threat to human and animal health (World Bank, 2016; FAO, 2016). Often, changing animal production systems modify and increase transmission of zoonotic disease infections in animals and humans (Richter et al., 2015). Drivers of changes in agricultural systems include new or adapted regulations and policies on agricultural and veterinary practices (Brooks, 2010; Weiss et al., 2004; Richter et al., 2015). National policies or a lack of policies, can exacerbate infectious disease emergence and re-emergence events (Perry et al., 2008; Otte et al., 2007). One region that is experiencing significant changes in its animal production systems is Southeast Asia. This region is experiencing rapid economic growth and dramatic increases in animal production and consumption (Devanandra et al., 2013). Population growth, urbanization and income growth are the key drivers of the increasing demand for livestock products and these three influencing factors are projected to increase for the next three decades (Thornton, 2010).

Governments in many countries in Southeast Asia set targets for livestock production and establish agricultural policies to reach these targets. For instance, in Lao PDR (Laos), the government is working to increase livestock production to reduce poverty and increase meat consumption from 22 to 50 kg per person in rural areas and 33 to 70 kg per person in urban areas (Theungphachan, 2008). Laos has promoted livestock production through national policies such as the Livestock Development Plan enacted through the Ministry of Agriculture and Forestry (Millar & Photakoun, 2008). Under this plan, livestock production is supported through national vaccination programs, animal disease response and prevention activities and training in livestock management for small-scale farmers.

Policies to promote livestock production are often effective at increasing animal production, however, changes in agricultural policies and animal production systems can have considerable positive and negative impacts on social equity, public health, natural resources and the economic growth of countries (Otte et al., 2007; Keesing et al., 2010; Perry et al., 2008; Jones et al., 2008). An important unintended consequence of the intensification of animal production includes increasing infectious disease and emergence events such as antimicrobial resistance (AMR) (Greger et al., 2007; Keesing et al., 2010).

Brucellosis

One example of agricultural policies and changes in agricultural production influencing the re-emergence of an infectious disease is brucellosis in Thailand. Brucellosis poses a significant public health problem in many regions of the world, particularly in low-income countries. The disease is commonly misdiagnosed as other febrile illnesses such as malaria, dengue or typhoid fever (Dean et al., 2012; Bamaiyi et al., 2014). Brucellosis also known as undulant fever, Malta fever, Crimean fever, and Mediterranean fever, is a zoonotic disease caused by bacteria of the genus *Brucella* (Seleem et al. 2010). There are several known species of the *Brucella* organism and some of these are pathogenic to humans (Seleem et al. 2010; Godfroid et al., 2011). The most virulent to humans and widely distributed species of *Brucella* is *Brucella melitensis (B. melitensis)* whose primary animal hosts are sheep and goats (Godfroid et al., 2011). Although *B. melitensis* is the most virulent among the *Brucella* species, any species of *Brucella* can potentially cause severe complications in humans (Seleem et al. 2010).

B. melitensis in humans can present mild to severe symptoms depending on the course and timeliness of treatment (Srinoy et al., 1999). The *Brucella* organism evades the immune system through intracellular localization, causing chronic illness and disability if left untreated (Roth et al., 2003). *B. melitensis* can cause fever, sweating, fatigue, weight loss, headache and joint and muscle pain (Seleem et al. 2010; Dean et al., 2012). Joint and muscle pain are often considered clinical manifestations that distinguish brucellosis from other febrile illnesses (Seleem et al. 2010). The most common complication among clinically diagnosed brucellosis patients is osteoarticular disease (Rotes-Qurol, 1957). The true rate of osteoarticular disease from brucellosis is unknown and global estimates range from 10% - 85% among those with a clinical diagnosis (Seleem et al. 2010; Rotes-Qurol, 1957). Spondylitis (inflammation of the vertebra) is the most prevalent and severe clinical form of osteoarticular disease (Rotes-Qurol, 1957).

The most severe complication in humans, *Brucella* endocarditis, occurs in less than 2% of cases and is the most common cause of death from the disease (Madkour, 2001; Gunes et al., 2009). Brucellosis poses a significant risk to pregnant women as it can cause spontaneous abortion or intrauterine transmission to the infant (Seleem et al. 2010). Brucellosis typically causes reproductive issues in animals including abortion, premature births, decreased fertility and retained placenta (Corbel, 2006). Other common symptoms in animals can include decreased milk production, lameness, mastitis, arthritis, epididymitis, hygromas and abscesses (Seleem et al. 2010). Clinical manifestation of brucellosis in animals or humans is not always specific and diagnosis supported by laboratory tests is essential to confirm a case (Seleem et al. 2010).

Infected animals excrete *Brucella* in urine, milk, placenta, and the products of miscarriage (OIE, 2012). Typical transmission to humans occurs via direct contact with infected animals, placentas or aborted fetuses, or consumption of infected animal products, primarily non-pasteurized milk products or insufficiently cooked or raw meat (Laosiritaworn et al., 2007). Butchering can pose a risk for transmission if personal protective equipment is not used when in contact with an infected animal's blood, fluid or tissue (Seleem et al. 2010). *Brucella* can survive for up to three weeks in frozen meat and up to three months in goat cheese (Molavi et al., 2014). Human to human transmission is very rare although it can occur through blood transfusion, tissue transplantation, breast-feeding, or sexual contact (Ruben et al., 1991). Infection can also occur through skin lesions, conjunctivae or from inhaling contaminated dust or aerosols (Spink, 1956).

Recommended treatment in uncomplicated acute brucellosis in humans includes combination therapy with antibiotics such as tetracycline or doxycycline administered in conjunction with an amino-glycoside such as streptomycin or gentamicin (Seleem et al. 2010). In uncomplicated cases, antibiotic treatment should last up to six weeks. In complicated cases, antibiotic treatment usually lasts twelve weeks to six months and includes at least three drugs (Yousefi-Nooraie et al., 2012). Treatment in pregnant women is difficult as recommended drugs have adverse effects on the fetus (Seleem et al. 2010). There is no known treatment for brucellosis infection in animals (Anothaisinthawee et al., 2012). Prevention of brucellosis in animals can occur through vaccination and agricultural practices (Anothaisinthawee et al., 2012). Vaccination has failed to control brucellosis in low-income countries due to high expense and limited accessibility (Blasco et al., 1997). There is a rising risk of brucellosis infection globally with the increasing rate of international travel, migration and commerce (Dean et al., 2012). According to a 2013 study of returned travelers to Europe and the U.S. from the Middle East and North Africa, brucellosis was the third most common cause of febrile illness (Leder et al., 2013).

There were no reported human cases of brucellosis in Thailand from 1970 until 2003 when three cases of *Brucella melitensis* in small-scale goat farmers were reported (Chiewchanyont et al., 2011). Brucellosis is currently considered endemic and human and animal brucellosis is now a notifiable disease in Thailand (Chiewchanyont et al., 2011). Literature reports varying levels of the disease in humans however, researchers estimate that 80% of all cases are related to exposure to goats (Chiewchanyont et al., 2011). A 2012 study in Nakhon Nayok province found that 45.33% of goat farmers sampled had seropositive antibodies to *Brucella melitensis* (Ekpanyaskul et al., 2012). According to the Thai Bureau of Epidemiology National Surveillance System, the current incidence in Thailand is between 5 and 11 reported and confirmed human cases per year (Thai Bureau of Epidemiology, 2016). Estimates for other *Brucella* species specific seroprevalence in humans were not identified.

One potential contributing factor to the re-emergence of brucellosis has been the substantial increase in goat farming throughout Thailand (Nakavisut et al., 2014). The number of registered goats in Thailand has increased from 177,944 in 2002 to 444,744 in 2007, representing a 2.5-fold increase (Nakavisut et al., 2014). Since the early 2000s the Thai government has promoted the expansion of small-scale goat farming through agricultural policies that encourage goat rearing (Nakavisut et al., 2014). These policies were primarily created to increase Muslim food production with goat farming originating in the southern part of Thailand but have since expanded throughout the country (Nakavisut et al., 2014). Goats are promoted as a profitable livestock to supplement household income for low-income farmers throughout low- and middle-income countries because of their low maintenance costs and grazing habits (Devendra et al., 2013; Anothaisinthawee et al., 2012).

In Thailand, most goat farmers left rice farming to enter into animal husbandry for greater economic benefits (Laosiritaworn et al., 2007). The majority of goat farms in Thailand are relatively small in scale averaging between 15-20 goats per farm (Anothaisinthawee et al., 2012).

Goats in Thailand are primarily used for their meat with consumption of goat milk becoming increasingly more popular as well as the use of goat placenta in cosmetic products (Anothaisinthawee et al., 2012).

Despite the re-emergence of brucellosis in humans in Thailand, a limited number of studies have been conducted that examine small-scale farmers and their knowledge, attitudes and behaviors towards the disease. The majority of research on brucellosis in Thailand has focused on seroprevalence in cattle on large-scale dairy farms. This has contributed to a gap in knowledge on brucellosis in goat husbandry compared to other species in Thailand (Bordier et al., 2013). There is a need for better-designed studies to further the evidence base for more effective prevention and control efforts (Plumb et al., 2013).

Antimicrobial Resistance

Another emerging global health and occupational threat to animal production workers influenced by the intensification of animal production systems is AMR. Antimicrobials refers to a broad class of drugs manufactured to kill or halt the growth of microorganisms. AMR occurs when microorganisms become resistant to drugs manufactured to kill the organism or halt its growth (WHO, 2012). Antimicrobials are becoming increasingly ineffective at killing microorganisms due to the spread of AMR (CDC, 2013). This emerging threat poses a risk to human and animal health as it can lead to an increase in infectious diseases, difficulty in treating common infections, uncertainty in success of surgical procedures and significant economic losses (Ventola, 2015).

All antimicrobial use contributes to the growth and spread of AMR however, an area of concern is the misuse and overuse of antimicrobials in livestock production. Antimicrobials are used in animal (terrestrial and aquatic) production systems throughout the world. In intensive food-animal production settings antibiotics are routinely used for nontherapeutic purposes mainly disease prevention and growth promotion (Van Boeckela et al., 2015). Critically important antibiotics for humans, such as colistin, are routinely used in animal production in certain countries (Nhung et al., 2016). Antimicrobials are often inexpensive and readily available for use in animals (Nhung et al., 2016). In many countries farmers and producers can purchase antimicrobial drugs over the counter and are often given limited instructions and information about the drug. Additionally, there is limited control and regulation to ensure the quality of the drugs (Gelband & Delahoy, 2014).

Antimicrobial use in agriculture is of concern for human health because it increases the risk for AMR and because antimicrobial-resistant microorganisms in livestock spread to humans in multiple ways. Resistant bacteria as well as antimicrobial residues from food-animal production can be spread widely in the environment with treated animals excreting active, unmetabolized antimicrobials. Agriculture workers are particularly vulnerable to AMR as they have a very high exposure risk through direct contact with infected animals and through indirect exposure through the environment (Marshall et al., 2011).

Antimicrobial resistance (AMR) poses significant economic threats to animal production systems because of potential adverse trade outcomes from contaminated animal product exports and negative impacts on animal health. AMR is expected to lead to reductions in global Gross Domestic Products, increases in poverty including an increasing inequality between high and low income countries and a decline in global livestock production (Ventola, 2015). The World Bank estimates that AMR “directly undermines the prospect for attaining the Sustainable Development Goal for 2030 to reduce inequality” (World Bank, 2016). It is estimated that by 2050, AMR in humans could lead to 10 million deaths per year and cumulative lost outputs worth up to US $100 trillion across the world (O’Neill, 2016).

With an international food trade exceeding 200 billion USD annually, agriculturally-linked AMR presents a global threat to public health, food safety, and livestock-based livelihoods (World Bank, 2016). Occupational threats of AMR can also pose a population-level risk as farmers and their families providing a conduit for further spreading AMR infectious diseases in communities and hospitals (Mølbak et al., 1999; Loeffen et al., 2005). Farmers are also vulnerable to the economic impacts of AMR due to losses in animal production with increasing ineffective antimicrobials for treating different diseases and adverse trade impacts (WHO, 2016).

AMR is of particular concern in Southeast Asia where a significant proportion of the population is dependent upon livestock production (Richter et al., 2015). AMR in animal pathogens and the loss of antimicrobials carries significant economic and food security risks for this region (Richter et al., 2015). Countries in Southeast Asia are also subject to a growing market for counterfeit and sub-quality antimicrobials (WHO, 2010). It is estimated that as high as 60% of antimicrobials used in Asia and Africa are substandard (World Bank, 2016). These practices are alarming as any use of antimicrobials accelerates the rate of AMR (Centre for Science and the Environment, 2017; World Bank, 2016). Effectively addressing AMR presents significant challenges due to its complex and multi-sectoral nature. Finding affordable strategies and tools to manage AMR in low- and middle-income countries is particularly important because of limited resources and evidence based solutions.

Limited actions have taken place among countries in Southeast Asian to address AMR. Many countries in this region have inadequate capacity including weak legal and regulatory frameworks and insufficient financial and human resources to effectively address AMR. Countries often have minimal regulation, laws or guidelines to promote rationale and responsible antimicrobial use and insufficient guidelines and regulations on infection prevention and control at the farm level. In order to strengthen policy response it is important to understand what policies have already been enacted to address AMR in animals and agriculture. Studies in this dissertation seek to better understand national regulatory frameworks to address AMR that have been established in countries in Asia.

Research objectives

This dissertation concentrates on two important emerging trends in animal food production posing public health and occupational risks. These trends include the increasing use of antimicrobials and the re-emergence of a zoonotic disease, brucellosis. Agricultural policies influence the expansion of small-scale animal husbandry and impact emergence and re-emergence of infectious diseases. The goal of this analysis is to understand the role of policy and its impact on influencing these two important emerging disease trends. There are four research aims in this thesis with each addressed in a chapter.

Specific Aim 1

Examine the knowledge, attitudes and livestock practices related to brucellosis among small-scale goat farmers. Chapter 2 is a cross-sectional study of small-scale farmers in Ratchaburi Province, Thailand. Farmers' attitudes, experience and behaviors towards brucellosis were measured along with serological testing for brucellosis in goats. The purpose of this study is to identify the potential determinants of exposure and occupational risk to brucellosis among goat farmers. The hypothesis of this study is that small-scale farmers have limited knowledge and awareness of brucellosis and that goat farming poses an occupational risk for human infection of brucellosis.

Specific Aim 2

Estimate herd and animal level seroprevalence of brucellosis in small ruminants in Thailand and determine which regions have the highest rates of infection. Chapter 3 analyzes national brucellosis surveillance data collected in Thailand from 2013 – 2015. The purpose of this study is to estimate national seroprevalence of brucellosis at the animal and herd level among small ruminants and to describe the spatial distribution of brucellosis throughout the country during a three-year period.

Specific Aim 3

This study identifies policy response to antimicrobial resistance (AMR) and analyzes policies related to antimicrobial use (AMU) and resistance from Indonesia, Cambodia, Myanmar, Lao PDR and Viet Nam. The purpose of this study is to analyze and describe countries' current regulatory framework to address AMR and AMU. The hypothesis of this analysis is that governments in Southeast Asian countries have yet to put in place a comprehensive and coherent legal and regulatory framework to protect public and animal health from AMR.

Specific Aim 4

Qualitative methods were used to analyze twelve countries regulatory frameworks to address antimicrobial resistance (AMR) and antimicrobial use (AMU) in animals and agriculture. Countries were from South Asia, the Pacific and Southeast Asia. This analysis provides information on countries awareness of existing policy to address AMR and AMU, future policy plans and overall national regulatory frameworks.

Significance

Overall, these studies contribute to our knowledge and understanding of how agricultural, health and public policies contribute to a system that can influence emerging trends in animal food production, including the spread of infectious diseases. Agriculture policies implemented by governments can have a direct and indirect consequence on occupational health risks particularly to farmers in low and middle income countries. The first study in this dissertation on brucellosis knowledge, attitudes and behaviors provides an example of the risk of the spread of a zoonotic disease at the farm level. The second analysis estimates the seroprevalence of brucellosis at the animal and herd level among small ruminants to understand how these trends are changing over time and by region and the direct impact of agricultural policies in Thailand.

The last two analysis of this dissertation, Chapters 4 and 5, describe the policy gaps and policy solutions, goals and benchmarks for national policies to address antimicrobial use and resistance. The rationale for these analyses is that understanding the consequences of agricultural policies provides informed recommendations for public and veterinary health management and prevention of diseases such as AMR. Understanding the interaction between agriculture legislation and policy, animal husbandry practices and occupational risks is an important step in controlling infectious diseases in Southeast Asia and around the world. Research from this dissertation highlights some of the challenges of infectious disease prevention and control. Studies from this dissertation provide a basis for future studies on agricultural and public policy for more effective control efforts for emerging and re-emerging threats in low- and middle-income countries.

Chapter 2:

Knowledge, attitudes and practices associated with brucellosis among small-scale goat farmers in Thailand

Summary

Background

Brucellosis re-emerged in humans in Thailand in 2003 with most infections occurring in in goat farmers. Research reports varying levels of the disease in humans with some estimates as high as 45.33% seroprevalence in goat farmers (Ekpanyaskul et al., 2012). Limited studies have been conducted to estimate seroprevalence of the disease in goats and to better understand farmers behaviors and experience with the diseases.

Methods

To better understand Thai farmers' knowledge, attitudes and behaviors associated with brucellosis a cross-sectional study was conducted during a three-month period in 2016 and included goat farmers living in rural and peri-urban areas of Ratchaburi Province in western Thailand. Fifty-one farmers were interviewed using a questionnaire that gathered information on demographics, understanding, attitudes and practices related to brucellosis and goat farming.

Findings

All serological samples collected from goats tested negative for brucellosis. Most respondents had limited experience with goat farming as over half (53%) reported owning goats for five or fewer years. The majority (80%) of farmers had heard of brucellosis but had limited knowledge of the disease in animals other than in goats, and limited understanding of disease transmission and symptoms. Knowledge of human brucellosis was particularly limited with just over half (54%) reporting that humans could become infected and less than half correctly identifying a symptom of the disease in humans. Participants had a very low perceived risk of infection with the majority reporting that they or a member of their household were not at risk of the disease. The majority of farmers reported limited use of personal protective equipment with fewer than a quarter reporting wearing gloves when in contact with livestock.

Conclusions

This study contributes to a more comprehensive understanding of brucellosis in Thailand by identifying specific human risk exposure to the disease through animal husbandry practices. Similar to previous research this study found that brucellosis poses an occupational risk as farmers engaged in high risk behaviors including minimal use of personal protective equipment and taking limited actions to assure a goat was healthy before purchase. Additionally, this study identifies areas where knowledge of brucellosis could be strengthened through farmer education and training.

Introduction

Brucellosis poses a significant public health risk in many regions of the world, particularly in low and middle income countries (Corbel, 2006). This zoonotic disease is caused by bacteria of the genus *Brucella* (Corbel, 2006; Seleem et al., 2010). The most infectious and common species of *Brucella* is *Brucella melitensis (B. melitensis)* whose primary animal hosts are sheep and goats (Corbel, 2006; Godfroid et al., 2011). *B. melitensis* in humans can present mild to severe symptoms causing fever, sweating, fatigue, weight loss, headache and joint and muscle pain (Corbel, 2006; Dean et al., 2012). The disease poses a significant risk to pregnant women as it can cause abortion or intrauterine transmission to the infant (Spink, 1956). In animals, brucellosis typically causes reproductive issues including abortion, premature births, decreased fertility and retained placenta (Corbel, 2006). Laboratory tests are essential to confirm a case of brucellosis in humans and animals as symptoms are varied and often non-specific (Molavi, 2012; Corbel, 2006). Infected animals excrete *Brucella* in urine, milk, placenta, and the products of miscarriage (Laosiritaworn et al., 2007). Typical transmission to humans occurs through direct contact with fluids from animals including placentas or aborted fetuses, or consumption of infected animal products, primarily non-pasteurized milk products or insufficiently cooked or raw meat (Laosiritaworn et al., 2007).

Literature suggests that expansion of animal husbandry programs and a lack of agricultural training and regulation contribute to a re-emergence of brucellosis in different parts of the world (Morse, 1995). One country that has experienced a re-emergence of human brucellosis is Thailand. There were no reported human cases of the disease in Thailand from 1970 until 2003 when two cases of *B. melitensis* in goat farmers were identified (Paitoonpong et al., 2006; Danprachankul et al., 2009; Chiewchanyont et al., 2011). The current incidence in Thailand is between 5 and 11 reported and confirmed human cases per year according to the Thai Bureau of Epidemiology National Surveillance System (Thai Bureau of Epidemiology, 2016). Human brucellosis is currently considered endemic to Thailand and one potential contributing factor to the re-emergence of brucellosis is the substantial increase in goat farming throughout the country (Wongphruksasoong et al., 2009; Nakavisut et al., 2014). Most cases of brucellosis in humans occur in goat farmers or are related to exposure to goats (Wongphruksasoong et al., 2009; Nakavisut et al., 2014). From 2002 to 2007 the number of registered goats in Thailand has increased from 177,944 to 444,744 (Chiewchanyont et al., 2011). In 2014, the Thai Department of Livestock Development (DLD), estimated that there were 41,674 goat farmers throughout the country (Kanitpun, 2014). The Thai government has promoted goat farming in Thailand through agricultural policies that support goat rearing through initiatives such as free insemination and vaccination (Nakavisut et al., 2014). Goats in Thailand are primarily used for their meat with consumption of goat milk becoming increasingly more popular as well as the use of goat placenta in cosmetic products (Anothaisinthawee et al., 2012).

Despite the re-emergence of brucellosis in Thailand, a limited number of studies have been conducted that examine small-scale goat farmers and their knowledge, attitudes and practices associated with the disease (Bordier et al., 2013). In 2003, the Thai Bureau of Epidemiology with the Thai DLD, investigated human brucellosis cases to identify risk factors for infection. Researchers categorized exposure to brucellosis as an occupational risk for goat farmers (Thai Bureau of Epidemiology, 2003). In 2009, Thai researchers reviewed human cases of brucellosis reported from 2003 to 2008 throughout the country and determined that all but two of the cases were associated with exposure to goats (Chiewchanyont et al., 2011). In 2012, investigators conducted a study among goat farmers where an outbreak of human brucellosis had previously occurred and determined that knowledge and perception of brucellosis was very poor and that there is a need for more effective training to prevent the disease in goats and other animals (Inchaisri et al., 2012). The objective of this study is to better understand the determinants of exposure to brucellosis associated with goat farming by assessing knowledge, attitudes and practices related to brucellosis among small-scale goat farmers.

Methods

Study design

Between June and August 2016, 53 small-scale goat farmers living in rural and peri-urban areas of Ratchaburi Province, Thailand were recruited to participate in this study. Participants recruited for this study were selected from a roster of farms registered with the Thai DLD. Inclusion criteria for recruitment were famers who owned 200 or fewer goats, were the person primarily responsible for the daily management of the farm and whose households were directly on the farm. Of the 53 participants, 51 farms were included that met the inclusion criteria and agreed to patriciate. Ratchaburi Province was selected as the study area because it is mostly agricultural with a high concentration of small-scale goat farms and is an area where previous outbreaks of brucellosis have occurred in goat farmers (Te-chaniyom et al., 2015).

Study teams included two or more veterinarians, provincial DLD officers and trained interviewers. Study teams visited each farm, gathered serological samples from goats and conducted interviews with farmers. Prior to participation in this study, respondents were orally informed about the research and provided written consent before participation. Approval to carry out the study was obtained from the University of Minnesota's Institutional Review Board and Chulalongkorn University's Ethics Review Committee. Approval for the animal study was obtained from Chulalongkorn University and University of Minnesota Institutional Animal Care and Use Committees. Additionally, approval was obtained from the DLD.

Survey methods

Farmers were interviewed using a 55-item questionnaire gathering information on demographics, knowledge, attitudes and practices relating to brucellosis. Questions were adapted from several studies assessing attitudes, knowledge and practices related to brucellosis among small-scale farmers (Holt et al., 2011; Montiel et al., 2013). The questionnaire was administered orally in the participant's native language, Thai, by a trained interviewer. Three of the interviews were conducted over the phone due to time constraints during the farm visit. Upon completion of the interview farmers were given a cash gift (300 Thai Baht). Participant interviews gathered information on participant demographics, risk factors, attitudes and knowledge of brucellosis, and goat and livestock ownership. Additionally, farmers experience with goat husbandry and barriers to the adherence of recommended husbandry practices were measured. Specific risk factors measured included grazing system, breeding practices, consumption of goat products and herd size. Additional details gathered about the goats included sex, age, and breed. Variables were measured as either continuous or categorical.

Serological testing

During farmer interviews, serological samples were collected from all goats at participating farms to estimate the seroprevalence of *B. melitensis* through the measurement of immunoglobulin G (IgG) antibodies. For identifying samples for testing, 15% of samples were randomly selected for testing from farms that had more than ten goats. This estimate was based on expected prevalence for the region according to DLD estimates. Samples were randomly selected based on codes randomly assigned during farm visits. For herds with less than ten goats all samples were tested. Following the World Organisation for Animal Health (OIE) standards, serological samples from goats were tested using the Rose Bengal Plate Test (RBPT) and the enzyme-linked immunosorbent assays (ELISA) test for *Brucella*. Serological testing took place at Chulalongkorn University Faculty of Veterinary Sciences Diagnostic Laboratories.

Data analysis

All data from the survey questionnaires and laboratory results were entered into Microsoft Office Excel 2015 (Excel, 2015). Data were analyzed using the statistical package STATA 14 (Stata Corporation, College Station TX, 2015). To examine knowledge, attitudes, and practices towards brucellosis to determine how these factors impact knowledge of brucellosis**,** models were run for each independent variable of interest and included multivariate logistic regression analysis of risk factors associated with knowledge of brucellosis. For the ELISA test, positive and negative controls were used to validate the test following the manufacturer's instructions. Each sample reaction from the ELISA was measured by an ELISA reader to determine the optical density (OD) at 450 nanometer. The ratio between the OD value for the sample and the OD value for the positive and negative controls were used to determine the S/P ratio. Serological samples were interpreted as positive with an S/P ratio greater than or equal to 120%**.** For the RBPT, following the manufacturer's instructions, serum was placed on a well of the test kit. An equal amount of antigen was placed on the sample and the mixture was gently moved consistently for four minutes and then observed for agglutination. If agglutination was observed, the sample was classified as positive, without agglutination the sample was classified as negative.

Results

Demographic characteristics

A total of 53 farms were visited during the study period from June to August, 2016. Among the 53 farms, 51 farms agreed to participate in the research that met the inclusion criteria. Over half (55%) of survey participants sampled were female and the majority (64%) reported primary school as their highest level of education completed. The most commonly reported age range was between 50-72 years old (51%). Most (63%) respondents reported having between 1 – 3 children under the age of 18 living at their household. The majority (80%) of respondents reported goat farming as their primary occupation and or their primary source of income. Table 2-1 describes the demographic characteristics of the respondents.

Table 2-1. Demographic characteristics of small-scale goat farmers in Ratchaburi Province, Thailand reported in a study on the knowledge, attitudes and practices associated with brucellosis in 2016 (n=51)		
Characteristic	(n)	(%)
Gender		
Male	23	45%
Female	28	55%
How many years have you lived in your current village or place of residence?		
10 or less	14	28%
11 – 30	13	25%
31 - 51	24	47%
How old were you at your last birthday?		
25 - 34	6	12%
35 – 49	19	37%
50 - 72	26	51%
How many adults (over the age of 18) are currently living in your household?		
1 – 4	34	67%
5 – 10	17	33%
How many children (under the age of 18) are currently living in your household?		
0	18	35%
1 – 3	32	63%
4 +	1	2%
What is your highest level of completed education?		
No education	1	1%
Primary school	32	64%
Secondary school	14	27%
Diploma	2	4%
Bachelor Degree	2	4%
Is your primary source of income and or primary occupation farming?		
Yes	41	80%
No	10	20%

Farm characteristics and livestock practices

Over half (53%) of the farmers reported owning goats for five or fewer years and the average farm size was 31 goats. The majority (86%) of farms reported owning at least one other type of animal including chicken (58%) or another type of poultry or both and a quarter (25%) of respondents owned cattle. The majority (92%) of farms reported grazing their goats at their household property and a third (30%) of respondents reported that they earned money renting out at least one of their goats to another farm in the past twelve months. Almost all (92%) respondents reported wearing or using at least one piece of personal protective equipment (PPE) when in contact with livestock. The most commonly reported piece of self-described PPE used was a long-sleeve shirt (92%). Less than a quarter (24%) of respondents reported wearing gloves when in contact with livestock. When asked the primary reason for not using PPE the majority (93%) of respondents reported that "there is no need for this equipment".

None of the participants reported consuming, selling or bartering meat, dairy or other products including placenta, from any of the goats they raised. All respondents reported that the primary purpose of their goats was for selling or bartering. When asked where or to whom they primarily sold their goats, more than a third (37%) reported selling to a merchant that purchased goats directly from their home. Sixty-six percent (66%) of farmers reported selling or bartering between 1 – 24 goats in the past 12 months. Over a third (33%) of farmers reported purchasing at least one new goat in the past twelve months. When asked where farmers purchased their goats, over half (61%) reported purchasing from a local market. See Table 2-2 for further details on farm characteristics and livestock practices.

Table 2-2. Farm characteristics and livestock practices among small-scale goat farmers in Ratchaburi Province, Thailand (n= 51)

Characteristic	(n)	(%)
How many years have you owned goats?		
1 - 5	27	53%
6 - 10	23	45%
11 +	1	2%
How many goats do you own?		
1 – 10	15	29%
11 – 20	15	29%
21 - 50	13	26%
51 - 200	8	16%
Where do you primarily graze your livestock?		
Household property	47	92%
Neighbors property	3	6%
Communal grazing land	1	2%
How many goats did you sell or barter in the past 12 months? (n=48)		
1 – 24	32	66%
25 – 49	10	21%
50 - 100	6	13%
If yes, where or to whom do you primarily sell your livestock to? (n=51)		
Local market	10	20%
Market in neighboring villages	2	4%
Livestock auction	1	2%
Relatives / friends / neighbors	19	37%
Merchant that purchases direct from home	19	37%
When you purchase goats, where do you purchase them from? (n =51)		
Local market	31	61%

Market in neighboring village	11	22%
Relative or friends	7	13%
Merchant	1	2%
Provincial Livestock Office	1	2%
During contact with livestock do you use the following protective equipment and or procedures? (n=47) ***Check all that apply***		
Boots	42	82%
Pants	26	51%
Long sleeve shirt	47	92%
Avoid drinking or eating	27	53%
Protective mask	37	73%
Gloves	12	24%
Goggles	3	6%

Goat health, treatment and prevention practices

Respondents were asked about their treatment and prevention practices specific to goat farming (Table 2-3). Almost all (90%) of participants reported that when they purchase a new goat they take actions to assure that the animal is healthy. Among those who reported taking actions when purchasing a new goat, almost a third (28%) reported that they require laboratory testing to make sure that the animal is healthy, almost a quarter (23%) require veterinary inspection and almost half (47%) rely on their own experience and judgement to determine if the goat is healthy. Less than a quarter (15%) of farmers reported quarantining the animal when they purchase a new goat. When asked what farmers do when a goat displays any signs of illness or disease, the majority (82%) of respondents give their goat(s) antibiotics and over half (53%) seek veterinary assistance. For the purposes of this study the Thai definition of a veterinarian was used which defines a vet as a licensed professional with a degree in veterinary medicine from an accredited institution.

Among respondents that do not seek veterinary assistance when a goat shows signs of illness or disease, the majority (96%) report that they do not believe this is necessary because they rely on their own personal experience and knowledge to treat the goat and the rest (4%) report not seeking veterinary assistance because the cost is too high. When asked how often respondents give antibiotics to their goats the majority (78%) report giving antibiotics to goats once a year while fewer than a quarter (18%) of respondents give antibiotics to their goats daily.

Almost all (96%) farmers reported that they did not give antibiotics to their goats when they are healthy. Seventy-five percent (75%) of respondents purchased their antibiotics at a pharmacy for animals, while less than a quarter (17%) purchased or were given antibiotics from a veterinarian. Two respondents reported that at least one of their goats had an abortion and or stillbirth in the last twelve months and both respondents reported burying the livestock fetuses. The majority (84%) of respondents reported burying their livestock carcass when an animal dies from illness. None of the 314 goat samples tested positive for *B. melitensis* for either the ELISA test for *Brucella* or the RBPT.

Table 2-3. Goat health, treatment and prevention practices among small-scale goat farmers in Ratchaburi Province, Thailand (n=51)

Characteristic	(n)	(%)
When you purchase or are given a new goat what action(s) do you take to assure that the goat is healthy? (n=47) ***Check all that apply***		
Trust in own experience and judgment	22	47%
Require laboratory tests	13	28%
Veterinary inspection	11	23%
Quarantine	7	15%
Sought expertise from experienced people in village	4	8%
Bought animals from persons you trust have healthy animals	4	8%
Paperwork indicated animal as healthy	2	4%
Inspection from seller	1	2%
What do you do if a goat is sick and/or shows signs of disease? (n=51) ***Check all that apply***		
Seek veterinary assistance	27	53%
Treat according to personal knowledge and experience	16	31%
Seek advice from friend/neighbor/ family	4	8%
Slaughter	0	0%
Isolate the animal	5	10%
Sell the goat	1	2%
Give the goat antibiotics	42	82%
When you use antibiotics, how often do you give them to your goats? (n=51)		
Daily	9	18%
Weekly	1	2%
Monthly	1	2%
Once a year	40	78%
Where do you purchase and/or are given antibiotics from? (n=43)		
Veterinarian	7	17%
Pharmacy for humans	3	6%
Pharmacy for animals	32	75%

Friends or neighbors	1	2%

Brucellosis knowledge and experience among farmers

The majority (80%) of respondents had heard of brucellosis. Among those who had heard of brucellosis more than a third (39%) reported learning about the disease from relatives or friends or both and the majority (98%) identified that goats were susceptible to brucellosis. Forty-one percent (41%) reported that cattle could become infected and 44% reported that sheep were susceptible to brucellosis. Over half (57%) reported that animals become infected with brucellosis through contact with aborted fetuses and placenta and all respondents who had heard of brucellosis correctly identified at least one symptom of the disease in animals. The majority (69%) reported that abortion was a symptom of brucellosis in goats and over half (53%) identified that decreased production could occur as a result of the disease in goats.

Among respondents aware of brucellosis, a little over half (54%) reported that humans could become infected. Over half (61%) reported that humans become infected through direct contact with livestock fetuses or fluids from infected animals. More than a third (38%) reported that they didn't know or were unsure if humans could become infected with brucellosis through mosquito bites and more than half (56%) reported that humans could not become infected by consuming unpasteurized (non-boiled) milk. Over half (58%) of respondents also did not believe humans could become infected by consuming undercooked or raw meat. Less than half (44%) of respondents could correctly identify at least one symptom of brucellosis in humans. See Table 2-4 for more information on respondents' knowledge of brucellosis. To estimate potential predictors of knowledge of brucellosis (such as has the farmer heard about brucellosis), univariate logistic regression analysis was used. Explanatory variables included gender, level of education, number of goats, years of farming, age and primary occupation. No association was found between knowledge of brucellosis and any of the predicator variables investigated.

Table 2-4. Knowledge of brucellosis among small-scale goat farmers in Ratchaburi Province, Thailand (n=51)		
Characteristic	(n)	**(%)**
Who or what is your primary source of information about brucellosis? (n=41) ***Check all that apply***		
Relative and or friend	16	39%
Veterinarian	13	31%
Book	10	24%
Radio	1	2%
Internet	0	0%
Village livestock meeting	12	29%
Which animals can become infected with brucellosis? (n=41)		
Cattle	17	41%
Sheep	18	44%
Goats	40	98%
Dogs	11	22%
Cats	10	20%
How do animals become infected with brucellosis? (n=41)		
Contact with urine or other bodily fluids from infected animal	11	27%
Licking infected animals	3	7%
Sharing a space with infected animals	7	17%
Contact with aborted fetuses and placentas	23	57%
Which of the following are symptoms of brucellosis in animals? (n=41)		
Abortion	28	69%
Premature births	4	10%
Swollen udders	1	3%
Swollen testicles	7	17%
Fever	16	39%
Retained placenta	1	2%
Infertility	11	27%
Decreased production	22	54%
Can humans become infected with brucellosis? (n=41)		
No	17	41%
Yes	22	54%
Don't know/unsure	2	5%
If yes, how do humans become infected from an animal?		
Consuming unpasteurized (non-boiled) milk? (n=36)	2	6%
Consuming undercooked or raw meat (n=36)	1	3%
Contact with infected livestock fetuses and fluids from infected animals? (n=36)	22	61%
What are the symptoms of brucellosis in humans?		
Fever (n=40)	17	42%
Arthritis (n=41)	4	10%
Aches (n=41)	4	10%
Chills (n=41)	2	5%
Joint and back pain (n=40)	1	2%
Sweats (n=41)	1	3%

Experience and attitudes associated with brucellosis

None of the respondents reported that they or any member of their household had ever been told by a doctor that they had brucellosis. Only one respondent reported having a case of brucellosis in at least one of their goat(s). The respondent reported that this case was confirmed and treated by a veterinarian. The respondent did not report culling the goat or having other livestock tested for the disease after the goat(s) was diagnosed with brucellosis. The majority (91.7%) of respondents do not believe they or any member of their household is at risk of brucellosis. Over half (62.5%) do not believe they are at risk of the disease because of safe farm practices. The majority (82%) believe that if one of their goats had brucellosis it would be quite serious and almost all (97.6%) respondents would like more information on the disease.

Discussion

Since the early 2000s the Thai government has promoted the expansion of small-scale goat farming through agricultural policies that encourage goat rearing (Nakavisut et al., 2014). These policies have contributed to an increase in goat farms throughout Thailand with a substantial number of new farmers entering the field of goat farming (Nakavisut et al., 2014; Anothaisinthawee et al., 2012). Although goat farming is a new occupation to them, for most it is their primary occupation and only source of income (Laosiritaworn et al., 2007; Chiewchanyont et al., 2011). This is significant when considering the importance of the goats' and farmers' health. Similar to previous research, this study found that brucellosis poses a potential occupational risk to goat farmers in Thailand (Laosiritaworn et al., 2003; Chiewchanyont et al., 2011; Anothaisinthawee et al., 2012). None of the respondents in this study reported consuming any products from their goats indicating that exposure to brucellosis could occur through other modes of transmission such as direct contact with fluids from animals rather than through consumption of milk or meat products (Chiewchanyont et al., 2011).

Farmers reported limited use of PPE when in contact with livestock. Limited use of PPE can be problematic as researchers have identified unprotected contact with placenta, blood and secretion as high risk factors for exposure to *B. melitensis* in Thailand (Thai Bureau of Epidemiology, 2003). However, use of PPE during high-risk situations such as during an disease outbreak or during birthing should be emphasized. In the US and Canada, goat farmers are encouraged to implement biosecurity efforts including use of PPE. Recommended PPE includes appropriate, clean and farm-specific outerwear and footwear for use when in contact with livestock. During an infectious disease outbreak farmers are recommended to wear plastic boots, gloves and coveralls, as well as fitted masks (Canadian Food Inspection Agency, 2013).

All farms included in this study housed goats and other animals on their immediate household property with very close proximity to households. This poses a potential risk for household members to come in contact with infected fluids from goats. Other high risk behaviors include not isolating an animal when it shows signs of illness or disease, renting out goats to neighboring farms and taking minimal action to assure a goat is healthy when purchasing a new animal. Farmers report that they often rely on their own experience and judgement to determine if an animal is healthy when purchasing a new goat with very few farmers requiring lab test or quarantining the new animal. This finding indicates that education for farmers on veterinary inspection, laboratory testing, and quarantine practices when purchasing a new goat might be useful in preventing the spread of brucellosis. Just over half of the farmers interviewed reported seeking veterinary assistant when their animal was sick while the majority (82%) responded that the first course of action to a sign of illness or disease in goats is to self-administer antibiotics to the goat. Potential overuse of antibiotics was also demonstrated with almost 20% of farmers reporting that they give their goats antibiotics daily. These findings demonstrate that education on responsible antibiotic use would be beneficial for this population.

Similar to previous research, this study found that although most farmers had heard of brucellosis, their knowledge of the disease was quite limited (Thai Bureau of Epidemiology, 2003). Most farmers identified that goats are susceptible to the disease but were less informed about other species susceptibility to brucellosis. Knowledge of human infection was less understood among farmers with just over half of respondents reporting that humans can become infected. Respondents demonstrated limited knowledge about how the disease is transmitted from animals to humans and had limited awareness of symptoms of the disease in humans. Over half of respondents did not believe humans could become infected by consuming undercooked or raw meat and less than half of respondents could correctly identify at least one symptom of brucellosis in humans. Like previous research conducted in other countries, the majority of respondents had low perceived risk of brucellosis infection in themselves or a member of their household (Lindahl et al., 2015). Farmers reported that they did not believe they are at risk because they have safe farm practices. Only one respondent reported having a confirmed case of brucellosis in at least one of their goat(s). This respondent reported that a veterinarian treated the goat and did report culling the animal or having other livestock tested for the disease. This finding suggests that additional education for veterinarians on best practices for management of brucellosis would be appropriate.

There is a need for more effective training to prevent the disease in goats and other animals and almost all the respondents in this study reported that they would like more information about the disease (Inchaisri et al., 2012). Farmer education and training on brucellosis including knowledge of disease transmission and symptoms in humans would be valuable. The most commonly reported source of information about brucellosis was from relatives or friends or both suggesting that interventions targeting peer education or goat farming networks could be effective at disseminating information about brucellosis.

Limitations

The sampling design used for identifying farms poses a limitation to this study. Farms were not randomly selected but rather identified based on routine DLD brucellosis testing. A selection bias may have occurred with the selected farms as they are all registered farms with the Thai DLD and may not be representative of the population of goat farms in Thailand. It is likely that the underrepresented farms are farms with few goats, thus routine animal husbandry practices may differ. This selection may also not be representative of the true seroprevalence of brucellosis in goats in Ratchaburi Province. Other issues inherent to this study include issues such as bias due to social desirability and relying on self-reported data gathered from the questionnaire.

Conclusions

This cross-sectional study contributes to a more comprehensive understanding of the knowledge, attitudes and practices associated with brucellosis among small-scale goat farmers in Thailand. Findings from this study support that brucellosis poses an occupational risk to goat farmers as farmers engage in high risk behaviors. Limitations in knowledge of the disease include limited awareness of disease transmission to humans and other species and lack of knowledge on safe farm practices such as quarantine practices when purchasing a new animal. Training on safe farm management practices, such as the use of PPE, is critical as the incidence of brucellosis and other infectious zoonotic diseases are influenced by farmers' experience, grazing practices, importation of animals, and the use of PPE (Lindahl et al., 2015). Prevention of the disease is particularly important in resource poor areas as treatment for human cases is expensive and often limited (Addis et al., 2015; Perry et al., 2002). Findings from this study are relevant for Thailand for improving the national brucellosis control program. Farmers expressed an interest in learning more about the disease. A unified approach that would involve both public health and veterinary sections would be beneficial realizing that brucellosis poses a health risk for both animals and humans.

Chapter 3

Seroprevalence of Brucellosis in Goats and Sheep in Thailand: Results from the Thai National Brucellosis Surveillance System from 2013 – 2015

Abstract

Brucellosis, a bacterial zoonotic disease, is commonly found in small ruminants in many parts of the world (Seleem et al., 2010; Corbel, 2006). The disease poses a public health risk in Thailand where it is endemic in small ruminants (Laosiritaworn et al., 2007; Thai Bureau of Epidemiology, 2003; Paitoongpong et al., 2006). In 1997 the Thai Department of Livestock Development (DLD) established a nationwide surveillance system for brucellosis in goats and sheep. We describe the seroprevalence of brucellosis in small ruminants in Thailand using these national surveillance data from 2013 – 2015. During the three-year period, 443,561 goats and sheep were tested for brucellosis by the DLD throughout Thailand using the Rose Bengal Plate Test (RBPT) and the enzyme-linked immunosorbent assay (ELISA) test for *Brucella*. Surveillance data collected included the number of animals and herds tested, the province of the animal and herd, and the laboratory results. Seroprevalence was estimated at both the animal and herd level. Overall, there was a decrease in the proportion of animals and herds that tested positive for *Brucella*. During the three-year period, 2013 had the highest proportion of herds that tested positive for brucellosis at 13.80% (95% CI, 12.52, 15.16). Provinces in the eastern and western regions of Thailand had the highest proportion of animals and herds testing positive during all three years and provinces in the south had the lowest. Periodic review of surveillance data documents the impact of the current brucellosis control program and supports a targeted response in higher prevalence regions when there are limited financial resources for control measures.

Introduction

Brucellosis, one of the most common zoonotic diseases, poses an occupational risk to livestock farmers in many parts of the world (Dean et al., 2012; Perry et al., 2002; Godfroid et al., 2011). This bacterial disease, also commonly referred to as undulant fever, Malta fever, Crimean fever, and Mediterranean fever, is caused by bacteria of the genus *Brucella* (Corbel, 2006). There are several known *Brucella* species some of which are pathogenic to humans. The most common *Brucella* species are *Brucella melitensis*, *Brucella abortus, Brucella suis,* and *Brucella canis* (Corbel, 2006). The most severe and common *Brucella* species in humans is *Brucella melitensis* (*B. melitensis*) whose primary animal hosts are sheep and goats (Godfroid et al., 2011). *B. melitensis* is most commonly spread between animals and to humans through direct contact with fluids from infected animals in birthing products and other bodily fluids such as urine (Corbel, 2006). Brucellosis is considered an occupational disease for those who work with animals generally from direct contact with contaminated birth fluids. Transmission to humans is primarily through consumption of un-pasteurized dairy products especially raw milk, soft cheeses, and butter (CDC, 2017; Corbel, 2006).

Common symptoms of *B. melitensis* in animals include abortions, stillbirths, infertility and decreased production (Corbel, 2006). Infection in humans can cause a range of symptoms common to febrile illness including joint and muscle pain, sweating, headache, fatigue and weight loss (Spink, 1956). The disease poses a significant risk to pregnant women as it can cause abortion or be transmitted to the infant in utero (Spink, 1956). The disease can additionally contribute to chronic illness and disability. (Addis, 2015, Perry, 2005). Severe cases of brucellosis in humans can result in endocarditis (Spink, 1956). Brucellosis is ranked as one of the top ten animal diseases of concern to impoverished rural communities (Perry, 2005).

There is increasing concern for the risk of brucellosis globally as the disease is re-emerging in certain countries where livestock production is increasing (Perry, 2002). Brucellosis is of concern in Thailand where the disease re-emerged in humans in 2003 (Laosiritaworn, et al, 2007). Two cases of *B. melitensis* in goat farmers were reported in Thailand in 2003 for the first time since the early 1970s (Laosiritaworn, et al, 2007; Chiewchanyont, et al., 2011). Brucellosis is considered endemic to Thailand and human and animal brucellosis are notifiable diseases (Chiewchanyont, et al., 2011). Understanding seroprevalence in small ruminants is important as research indicates that goats play a significant role in transmission of the disease to humans in Thailand. Paitoonpong et al. presented a case analysis of seven laboratory confirmed human cases of brucellosis in Thailand between 1970 and 2005 and determined that the majority of infections were a result of direct contact with goats (Paitoonpong et al. 2006). In 2003, the Thai Bureau of Epidemiology (BOE) with the Thai Department of Livestock and Development (DLD) investigated human brucellosis cases and categorized exposure to brucellosis as an occupational risk for goat farmers (Thai Bureau of Epidemiology, 2003). In 2009, Thai researchers reviewed 38 human cases of brucellosis reported throughout Thailand from 2003 to 2008 and found that all but two of the reported cases were associated with goats and one case was associated with contact with sheep (Chiewchanyont et al., 2011).

One potential contributing factor to the re-emergence of brucellosis has been the substantial increase in goat farming throughout Thailand (Nakavisut., 2014). Since the early 2000's the number of registered goat farms has more than doubled and continues to increase (Kanitpun et al., 2014). The increase in goat farming is partly due to government support for small-scale goat farming through agricultural policies that promote goat rearing (Srinoy et al., 1999; Nakavisut et al., 2014). Policies to encourage goat farming were created in part to increase Muslim food production with goat farming originating in only a few select provinces in the south (Satchaphun et al., 2014; Nakavisut et al., 2014). Goat farming has since expanded beyond the southern region and now occurs throughout Thailand with most farmers raising goats for their meat with goat milk becoming increasingly popular (Anothaisinthawee et al., 2012).

Additionally, goat farming was promoted as a profitable means to supplement household income for low-income farmers. Goat farming is common throughout low- and middle-income countries because of their low maintenance costs and grazing habits of poor arable lands (Devendra et al., 2013).

Since 2003 the Thai DLD has initiated several programs to control and prevent brucellosis in small ruminants (Ninprom et al., 2016). Activities include farm certification programs, free brucellosis testing, education and awareness campaigns, regulations to promote strict animal movement, policies for testing and slaughtering, and compensation schemes by the DLD (Sagarasaeranee et al., 2016; Nakavisut et al., 2014). The DLD policy for positive brucellosis tests includes culling the animal and testing the remaining animals in the herd every two months until three consecutive negative test results (Sagarasaeranee et al., 2016). Six months following the last negative test, the farm can be declared brucellosis free (Sagarasaeranee et al., 2016). In 1997, the DLD established a surveillance system for brucellosis for goats and sheep in Thailand. This system uses serological samples collected during annual brucellosis testing by the DLD at registered farms.

Despite the re-emergence of brucellosis in Thailand, a limited number of studies have been conducted that examine seroprevalence in small ruminants. Most research on seroprevalence has been concentrated to specific regions of the country. For instance, Ninprom et al., estimated seroprevalence of goats in the five most southern provinces of Thailand using data collected in 2014 from 15,281 goats from 845 herds (Ninprom et al., 2014). Ninprom et al. estimated herd level prevalence at 1.78% and animal level prevalence 0.44% (Ninprom et al., 2014). In 2008, Kaewket estimated seroprevalence of brucellosis at 11.5% in goats in the western region of Thailand (Kaewket, 2008). One study examined seroprevalence throughout Thailand and estimated prevalence at 12.1% (438/3,626) at the herd level and 1.4% (1,297/94,722) at the animal level (Sagarasaeranee et al., 2013). Using data from the national brucellosis surveillance system, this study reviews national seroprevalence at the animal and herd level among small ruminants and describes the spatial distribution of brucellosis throughout Thailand during a three-year period. An investigator led study of brucellosis in conjunction with the Department of Livestock Development (DLD) was also conducted in Ratchaburi province. The focus of this study is on seroprevalence in goats and sheep as these are the primary causes of brucellosis in humans in Thailand with as high as 80% of all human cases related to exposure to goats (Chiewchanyont et al., 2011). Ruminants and other animals can shed *Brucella* throughout their lifetime.

Methods

This study used sample results collected for the Thai National Surveillance System. The surveillance system includes test results from annual DLD brucellosis testing among sheep and goats at all registered farms for all small ruminants older than six months. Farms voluntarily register for brucellosis testing with the DLD, a department under the Thai Ministry of Agriculture. The DLD also provided population level data on the total number of goat and sheep herds available for testing throughout Thailand. This data includes both registered and non-registered farms with the DLD.

An investigator led seroprevalence study was conducted in Ratchaburi Province in western Thailand in 2016. This surveillance was part of another effort and is included in this analysis as a second source of information on brucellosis seroprevalence. The study tested 314 goats at 51 registered farms selected by the DLD. A serological sample was collected from every goat during the farm visits. For serological testing, 15% of samples from each farm were randomly selected for analysis from farms that had ten or more goats based on expected prevalence for the region from previous DLD estimates. For farms that had fewer than ten goats all samples were tested. Blood samples were tested at the Chulalongkorn University, College of Veterinary Diagnostic Laboratory. Additionally, serological samples tested by the DLD at a regional laboratory during the same timeframe and in the same province were obtained and compared. Serological testing followed the same DLD testing protocol at both laboratories. Approval to conduct this analysis was obtained from the University of Minnesota Institutional Animal Care and Use Committees and the Thai DLD.

Testing methods for laboratory serodiagnosis of brucellosis used by the DLD include the Rose Bengal Plate Test (RBPT) and enzyme-linked immunosorbent assay (ELISA) test for *Brucella*. The ELISA has a 98% sensitivity and 100% specificity and is a direct method for detection of specific antibody and therefore it is not prone to a false positive reaction. The RBPT is currently the recommended rapid screening test for *Brucella* with 100% sensitivity and 94.2% specificity.

All samples included in the surveillance system were analyzed at a DLD regional laboratory. An animal was considered *Brucella* positive if either the RBPT or the ELISA test was positive. A herd was defined as infected if it had at least one positive animal sample. The term 'herd' is defined by the DLD as a group of animals owned by the same farmer(s). To characterize prevalence across the country provinces were divided into six regions used by DLD; south, central, western, eastern, northern and northeastern regions.

Brucellosis prevalence at the herd and animal level was characterized by province and region. The precision of the prevalence estimates are described with 95% confidence intervals. The spatial distribution of brucellosis seroprevalence was further described at the provincial level for all three years using ArcMap 10.5 and is based on digital national maps of Thailand (ESRI, Redlands, CA). In these presentations the prevalence is presented as quartiles based on the prevalence distribution for all three years across the country. To characterize the relationship of brucellosis prevalence between regions and by year, herd-level prevalence rate ratios and 95% confidence intervals were estimated with Poisson regression. In these models the estimates were mutually adjusted for year and region. All analyses were completed using the statistical package STATA 14 (Stata Corporation, College Station TX, 2015).

Results

The DLD tested a total of 443,561 serum samples collected from sheep and goats from 10,843 herds between 2013 and 2015. Three thousand one hundred and seventeen (3,117) animals and 1,010 herds were identified as seropositive during the three year period. Samples were collected from 76 provinces in Thailand and the number of samples collected accounts for 27.3% of the total small ruminant population and 7.79% of the total small ruminant herd population. In 2013, the proportion of all goat and sheep that tested positive at the individual animal level was 1.39% (95% CI, 1.32, 1.46), 0.20% (95% CI, 0.01, .0.20) in 2014, and 0.81% (95% CI, 0.77, 0.86) in 2015. Nationwide, the proportion of positive herds in 2013 was 13.80% (95% CI, 9.86, 12.26), 8% (95% CI, 7.41, 9.23) in 2014 and 7.47% (95% CI, 6.72, 8.27) in 2015.

The seroprevalence for the entire country and all years at the animal level was 0.72% (95% CI, 0.68, 0.73) and 9.31% (95% CI, 8.77, 9.88) at the herd level. Provinces in the southern region of the country had the lowest proportion of animals testing positive for brucellosis compared to other parts of Thailand with an overall herd level seroprevalence of 2.93% (95% CI 2.4, 3.5) and .31% (95% CI .27, .34) animal level seroprevalence. Our estimates indicate that overall seroprevalence among provinces ranged from 0.31% (95% CI, .27%, .34%) to (1.12, 95% CI, 0.89%, 1.39%) at the animal level and 2.92% (95% CI, 2.44%, 3.5%) to 18.42% (95% CI, 1.32%, 2.47%) at the herd level. The seroprevalence of brucellosis at the animal and herd level is summarized by year and by region in Tables 3-1 and 3-2.

Table 3-1. Seroprevalence of brucellosis in sheep and goats at the animal level, by region in Thailand, 2013 – 2015				
Region	**Year**	**Animals tested**	**Positive animals**	**Animal seroprevalence**
Northern	**2013**	2482	3	0.12%
Northeastern	**2013**	6093	95	1.56%
Central	**2013**	18734	380	2.03%
Eastern	**2013**	1400	22	1.57%
Western	**2013**	45050	716	1.59%
Southern	**2013**	29621	220	0.74%
Total	**2013**	**103,380**	**1,436**	**1.27%**
Northern	**2014**	3920	2	0.05%
Northeastern	**2014**	4488	3	0.07%
Central	**2014**	34653	96	0.28%
Eastern	**2014**	2733	21	0.77%
Western	**2014**	98972	202	0.20%
Southern	**2014**	30806	21	0.07%
Total	**2014**	**175,572**	**345**	**0.20%**
Northern	**2015**	4401	23	0.52%
Northeastern	**2015**	7613	79	1.04%
Central	**2015**	36877	331	0.90%
Eastern	**2015**	2890	36	1.25%
Western	**2015**	71993	793	1.10%
Southern	**2015**	40835	74	0.18%
Total	**2015**	**164,609**	**1,336**	**0.82%**

Table 3-2. Seroprevalence of brucellosis in sheep and goats at the herd level, by region in Thailand, 2013 – 2015

Region	Year	Herds tested	Positive herds	Herd seroprevalence
Northern	2013	36	2	5.56%
Northeastern	2013	190	35	18.42%
Central	2013	488	79	16.19%
Eastern	2013	33	10	30.30%
Western	2013	949	169	17.81%
Southern	2013	999	77	7.71%
Total	**2013**	**2,695**	**372**	**13.80%**
Northern	2014	60	1	1.67%
Northeastern	2014	91	2	2.20%
Central	2014	742	82	11.05%
Eastern	2014	76	13	17.11%
Western	2014	1502	181	12.00%
Southern	2014	1150	21	2.00%
Total	**2014**	**3,621**	**300**	**8.29%**
Northern	2015	81	5	6.17%
Northeastern	2015	211	23	10.90%
Central	2015	699	74	10.59%
Eastern	2015	81	12	14.81%
Western	2015	1299	169	15.09%
Southern	2015	2156	28	1.30%
Total	**2015**	**4,527**	**338**	**7.47%**

Regional differences as a risk factor for brucellosis infection were investigated. A multivariable Poisson model with robust standard errors was used to model the count of *Brucella* positive animals and herds, with the number of herds and animals tested as an exposure variable and adjusted for year. Both model's pseudo r^2 suggests the fit was appropriate with values between 0.2 – 0.4 (McFadden, 1974). The year, 2013 was used as the reference group for the variable year. Due to its low seroprevalence at the herd and animal level the southern region was included as the reference group. Compared to the south, differences in seroprevalence were statistically significant for the western, eastern and central regions for the herd level seroprevalence. After controlling for year, herds in the eastern region had 2.34 times the prevalence of brucellosis compared to the southern region. For the animal level seroprevalence, the eastern, central and northeastern regions were statistically and nearing statistical significance different compared to the southern region.

Table 3-3. Prevalence ratios of animal seropositivity by region

Region	***Prevalence ratio***	**95% CI**
2013	1	-
2014	.13	(.09, .20)
2015	.58	(.41, .82)
Southern	1	-
Northern	0.41	(0.17, .94)
Northeastern	1.30	(0.96, 1.76)
Central	1.46	(0.94, 2.28)
Eastern	1.87	(1.23, 2.82)
Western	1.39	(0.86, 2.24)

Table 3-4. Prevalence ratios of herd seropositivity by region

Variable	***Prevalence ratio***	**95% CI**
2013	1	-
2014	0.50	(.31, .79)
2015	0.47	(.28, .78)
Southern	1	-
Northern	0.56	(0.29, 1.05)
Northeastern	1.31	(0.83, 2.04)
Central	1.44	(0.99, 2.09)
Eastern	2.34	(1.59, 3.44)
Western	1.72	(1.11, 2.67)

Spatial distribution of brucellosis is shown in Figures 2-1 and 2-2. Provinces in the eastern region of Thailand had on average the highest proportion of herds testing positive during a 3-year period. The second highest animal and herd level seroprevalence were detected in the western region. The western region had a herd level seroprevalence of 17.81% and an overall herd level seroprevalence of 13.84% in 2013 (see Table 3-2). Among provinces that had greater than ten herds, Kanchanaburi Province, in the central region of Thailand, had the highest proportion of herds that tested positive for brucellosis at 59.78% (95% CI, 49.04, 69.87) in 2013. The province with the highest proportion of animals testing positive at the individual animal level was Phichit, in the northern region, with 30.64% (95% CI, 24.8, 36.96) in 2013. This finding suggests that a substantial proportion of goat and sheep herds in these regions were actively or recently infected.

Fig. 2-1. Spatial distribution of the proportion of goats and sheep who tested positive for brucellosis at the animal level, Thailand, 2013 - 2015.

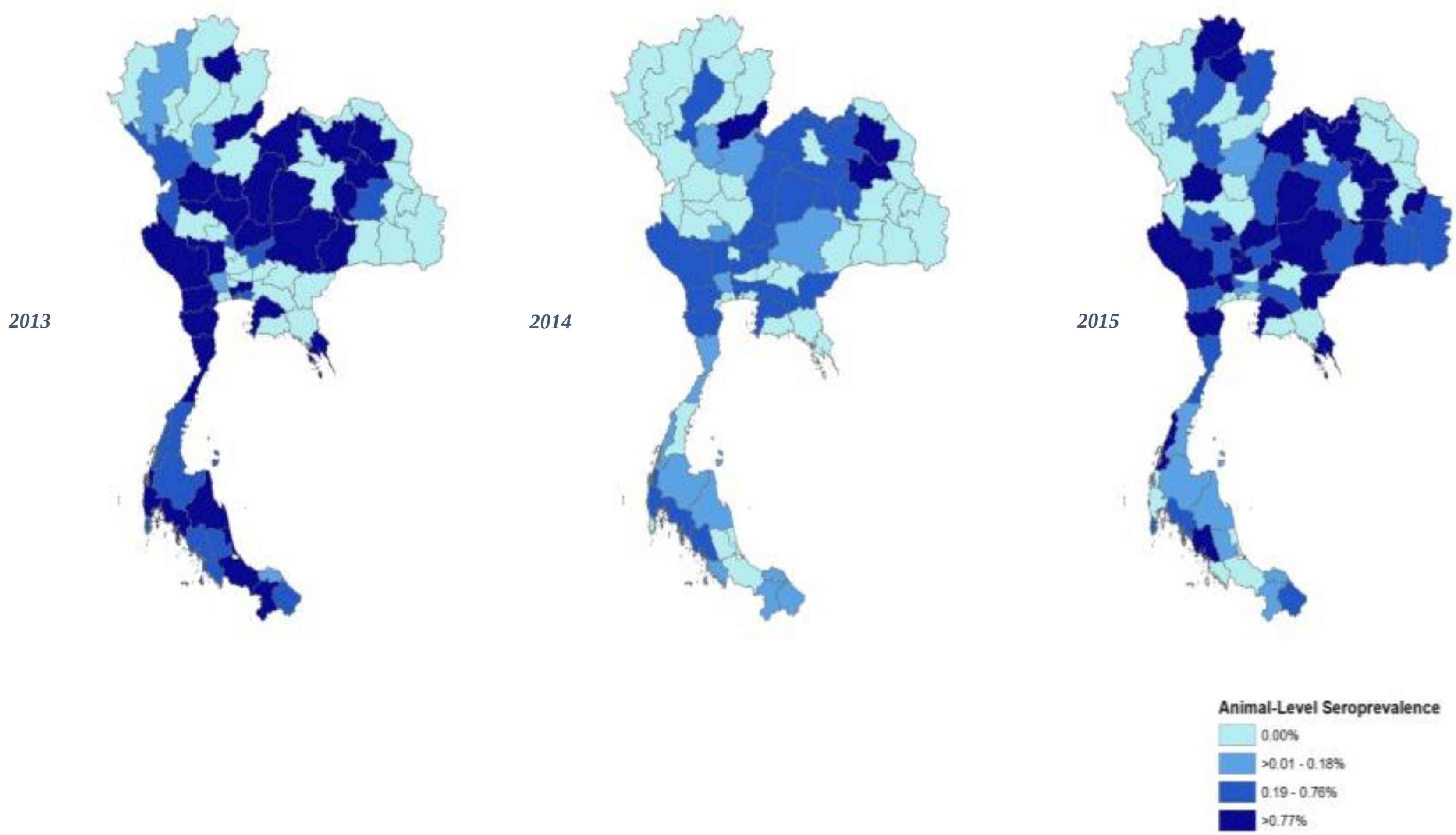
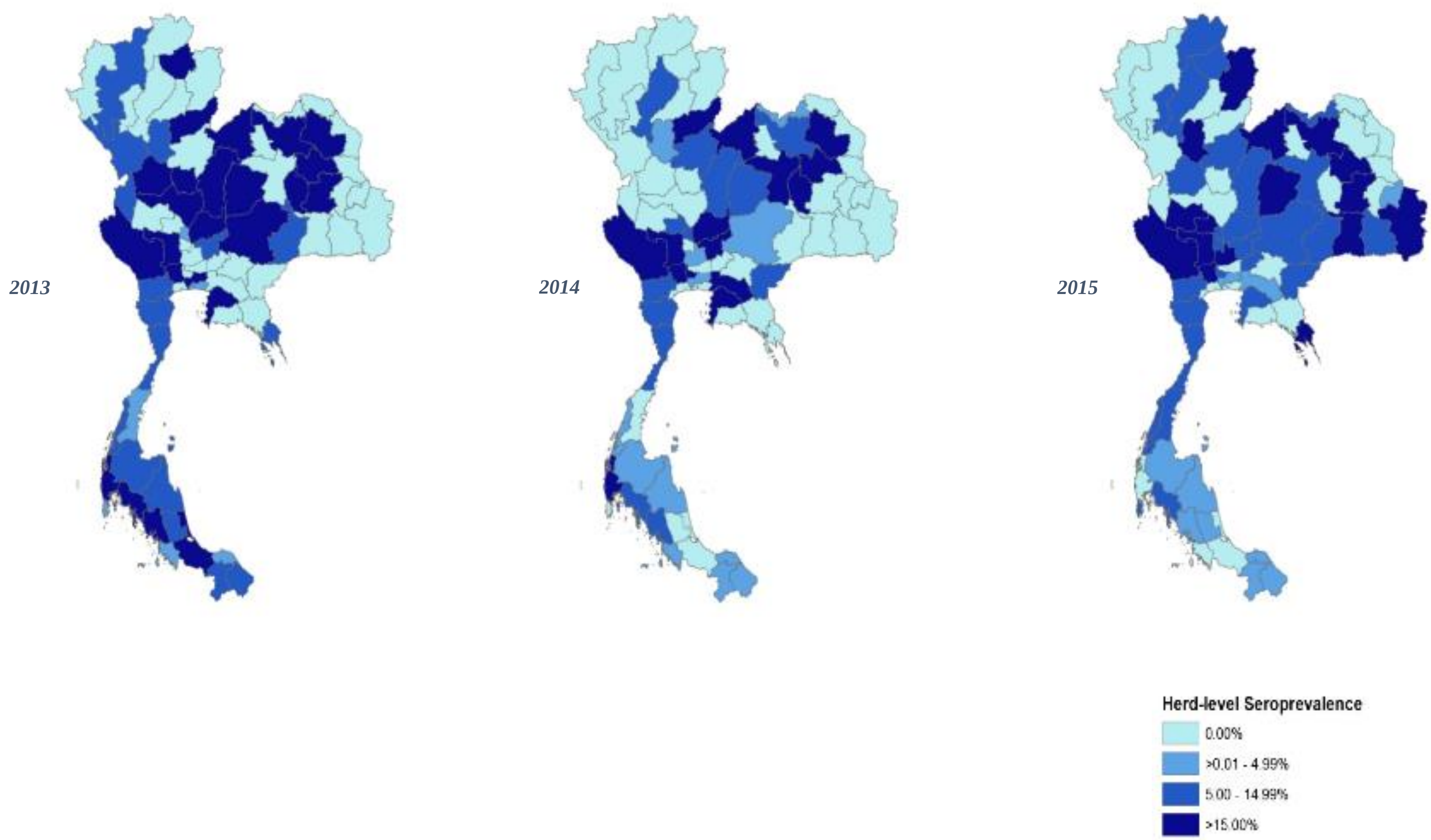


Fig. 2-2. Spatial distribution of the proportion of goats and sheep who tested positive for brucellosis at the herd level, Thailand, 2013 - 2015.



Province specific findings from the investigator study conducted in 2016 in Ratchaburi Province found varying results. Laboratory confirmed results from Chulalongkorn University veterinarian laboratory tested 314 samples and found all to be negative. The Thai DLD tested 119 samples collected during the same time-period and the same region and confirmed 4 tests to be positive estimating the proportion of positive goats to be 3.36% (95% CI, 0.92, 8.38).

Discussion

Using data from the Thai national brucellosis surveillance system, this study aimed to estimate the proportion of small ruminants that tested positive for *Brucella* at the animal and herd level from 2013 to 2015. This analysis indicates that overall the proportion of positive brucellosis cases is decreasing throughout the country at both the animal and herd level. These findings are consistent with previous research conducted by the DLD indicating that brucellosis in small ruminants is decreasing in Thailand (Sagarasaeranee et al., 2016). However, the high proportion of herd level seropositivity among the three-year period in the eastern and western regions suggest that prevention and control efforts could be enhanced in these areas for more effective brucellosis control. Provinces in the central region also experienced a high proportion of herds that tested positive. These are areas of concern as provinces in this region such as Kanchanaburi Province have previously experienced human brucellosis outbreaks (Sagarasaeranee et al., 2016; Danprachankul et al., 2009). Estimates from the western region are similar to Kaewket's findings from 2008 with 11.5% at the herd level compared to our herd level seroprevalence of 13.84% (Kaewket et al., 2008).

On average, farms in the southern provinces had the lowest seroprevalence at both the herd and animal level. It is worth noting that our results are comparable to previous research estimating seroprevalence in southern provinces. Our estimates are similar to Ninprom et al. who estimated seroprevalence at 0.44% at the animal level and 1.78% at the herd level in the south. However, this analysis contradicts previous research that identified the southern region of

Thailand as an area of high concern for brucellosis due to shared borders and high goat meat consumption (Baimiya et al, 2015; Ninprom et al., 2014).

Serological findings from province specific seroprevalence studies in Ratchaburi Province, were to be expected given the sample size. In 2015, the DLD tested 15,377 animals from 482 farms from this region and found a 0.66% seroprevalence at the animal level and 7.26% seroprevalence at the herd level. Ratchaburi Province overall had an average herd level seroprevalence of 8.87% and .70% animal level seroprevalence from 2013 - 2015. Ratchaburi Province has a high concentration of goat farms with nine out of ten districts in the province having goat farms (Te-chaniyom et al., 2015). This is also a province of concern as previous human brucellosis cases associated with goats have been detected in this region (Te-chaniyom et al., 2015).

The surveillance data demonstrate that the number of farms tested increased throughout Thailand from 2013 – 2015. For instance, the number of herds tested among all regions, more than doubled from 1,754 in 2013 to 4,572 in 2015. Provinces in the central and western regions of Thailand had the highest number of goats and sheep tested throughout the country with Nakhon Pathom, Ratchaburi and Kanchanaburi having the highest numbers of animals and herds tested from 2013 – 2015. Population level farm and animal data also indicate that goat and sheep farming is increasing throughout Thailand. The sheep and goat population increased 22.85% from 476,513 animals in 2013 to 585,387 in 2015. The number of herds increased by 2.64% during this time period indicating that the number of farms is not increasing at a high rate but rather individual farms maybe increasing the number of goats and sheep. The population level data indicate that the southern and western regions of Thailand have the highest number of goats and sheep among all the regions.

As goat farming continues to increase, potential human health consequences should be taken into consideration when adapting policies to promote animal husbandry. Policies to expand

and promote animal production should consider public health threats and ensure appropriate disease prevention and control initiatives are implemented. Policy-makers, veterinarians, farmers, physicians and other stakeholders in animal production should be aware of the re-emergence of brucellosis and the occupational risk for small ruminant farmers and their families.

Limitations for this analysis include a potential bias in using data collected for the surveillance system. Farms participating in the surveillance system were actively registered with the DLD and voluntarily agreed to be tested for brucellosis. These farms may not be representative of farms at the national level. An additional limitation of this data is the lack of information on farm level characteristics including the exact location of the farm within the province and information linking farms to herd.

Conclusion

This study characterized the seroprevalence of brucellosis in small ruminants in Thailand using data from the Thai National Surveillance System. Review of surveillance data is an important measure to understand the impact of brucellosis control efforts and to identify areas where targeted response is needed. Overall this study identified that brucellosis seroprevalence in small ruminants may be decreasing throughout Thailand. However, there is variability in the distribution of the disease with some regions experiencing significantly higher rates of disease than others. With the increasing goat population, potential human health consequences should be taken into consideration when adapting animal husbandry policy. Policies to control brucellosis should be continued and strengthened to further reduce brucellosis. The DLD should ensure that farmers have access to education and training opportunities on the prevention and control of brucellosis. Next steps for improving understanding of brucellosis in Thailand would be to investigate and document goat movement between countries and provinces. Findings from this study can be used to strengthen control efforts to improve the management of the disease in Thailand.

Chapter 4

Governance and policy to address antimicrobial resistance and antimicrobial use in animals and agriculture in Southeast Asian countries

SUMMARY

Policy plays a critical role in controlling and preventing the growth of antimicrobial resistance (AMR). A range of policy recommendations have recently been proposed to combat AMR at the national level (WHO, 2016; Dar et al., 2016; O'Neill, 2016). Understanding what national policies already exist is important to ensure informed policy recommendations are made. This analysis provides a deeper understanding of Southeast Asian countries' AMR and antimicrobial use (AMU) policy in food and agriculture. Policies and proposed strategies from Lao PDR, Myanmar, Viet Nam, Cambodia and Indonesia were compared. Key documents reviewed ranged from drafted and officially approved National Action Plans to food and animal production legislation, including animal husbandry regulation and pharmaceutical law. Regulations across four policy domains were examined: (1) governance; (2) infection prevention and control; (3) awareness and education; and (4) evidence. In total, the analysis reviewed over 230 policy documents directly or indirectly related to AMR and AMU.

The analysis revealed countries have existing policy that can be used to address AMR at the national level. Most countries have enacted pharmaceutical and animal husbandry laws to regulate the use of antimicrobials in animals and agriculture. Most countries require prescriptions for use of antimicrobials in animals, and most encourage responsible distribution of antimicrobials through advertising and labeling standards. Several countries prohibit counterfeit drugs and overselling antimicrobials. Many countries are also starting to implement bans of specific antibiotics for use in animals and have established policy goals to eliminate or restrict the nontherapeutic use of antimicrobials. With the development of National Action Plans to address AMR, many countries have the foundation to develop AMR/AMU awareness initiatives, to provide support for surveillance and monitoring systems, and improve infection prevention and control systems. Despite a plethora of existing policy, several limitations exist. Existing policies suffer from weak or nonexistent standards for limiting or reducing the use of critically important

and nontherapeutic use of antimicrobials. Most countries do not have legislation that specifically bans the use of antimicrobials for use as growth promoters or for disease prevention. Although data regarding enforcement is sparse, the effectiveness of existing policy is likely weakened as a result of insufficient enforcement capacity, infrastructure, and funding.

INTRODUCTION

Antimicrobial resistance (AMR) is one of the most significant global health threats (World Health Organization, 2015; Food and Agriculture Organization, 2016). AMR and antimicrobial use (AMU) present complex policy challenges requiring effective governance and coordination across sectors (Dar et al., 2016; Årdal et al., 2015; OECD, 2016). The 2016 O'Neill Review argues that if significant policy change does not occur, AMR related human deaths will increase to ten million worldwide by 2050 (O'Neill, 2016). Increased use of antimicrobials in animal husbandry pose a significant concern for potential spread of AMR to the environment and to humans (Hershberger et al., 2004; Speksnijder et al., 2014). There is increasing consensus that unnecessary use of antibiotics in animals and agriculture pose a significant concern for animal and human health (O'Neill, 2016). Antimicrobial resistant microbes carried by infected animals can transfer to humans through consumption of contaminated food, direct contact with animals, or through the environment (OECD, 2015; Landers et al., 2012; Ventola, 2015). Use of antimicrobials in the livestock production industry for therapeutic and nontherapeutic purposes, such as growth promotion and prophylaxis, is widespread across Southeast Asia (Nhung et al., 2015).

Significant drivers of AMR in this region include limited regulation and weak governance, including a lack of enforcement and compliance with policy (FAO, 2016; Gelband, et al., 2014; Landers et al., 2012). Governments often have limited capacity to fully implement policies due to a lack of technical capacity and inadequate financial resources (Gelband, et al., 2014; Landers et al., 2012). This is particularly problematic, as efforts to control the spread of AMR are primarily governance issues, and governments are the primary actor responsible for how countries respond to this threat (O'Neill, 2016).

AMR is becoming a top priority on political and policy agendas with a range of recommendations recently proposed (WHO, 2016; Dar et al., 2016). In 2015, the World Health

Assembly, in coordination with the World Organization for Animal Health (OIE), and the Food and Agriculture Organization (FAO), adopted a Global Action Plan (GAP) on AMR. The GAP outlines specific recommendations for countries to decrease and prevent the spread of AMR. A key recommendation of the GAP is the development of country specific National Action Plans (NAPs). The GAP expects all WHO Member States to develop their own NAP in line with the GAP by May 2017 (WHO, 2015).

To more effectively strengthen national AMR policy in Southeast Asia, understanding existing regulatory activities is essential. Using a set of policy benchmarks identified from key global AMR documents, this report compares and contrasts policy from Laos, Cambodia, Viet Nam, Myanmar, and Indonesia. Countries selected for this analysis have comparable animal production systems and regulatory frameworks and are at similar stages in addressing AMR in animals and agriculture (Nhung et al., 2015). Overall this analysis contributes to a more comprehensive understanding of whether governments have established policy that can be used to protect public and animal health from AMR.

RESEARCH DESIGN

This analysis was guided by a set benchmarks identified in key AMR guidance documents. Guidance documents reviewed included the World Health Organization (WHO) GAP on Antimicrobial Resistance, the FAO Action Plan on Antimicrobial Resistance, the Global Health Security Agenda Antimicrobial Resistance Action Package, the 2016 World Bank Report "Drug-Resistant Infections: A Threat to Our Economic Future", the 2016 O'Neill Review on AMR, the WHO Manual for Developing National Action Plans and others. Four policy domains were identified in these guidance documents: (1) governance including regulation of antimicrobials; (2) infection prevention and control; (3) awareness and education; and (4) evidence. Where necessary, policy subdomains further divide the analysis process. The guidance documents were also used to derive sub-domains and criteria to assess, compare, and contrast policies for each policy domain. These criteria are listed under each policy domain in Tables 4-1, 4-3 and 4-5.

Due to the nature and complexity of AMR, it is rarely embodied in a single, comprehensive, stand-alone policy. As a result, this analysis interprets the concept of AMR and AMU policy broadly in analyzing laws, regulations, and other soft-policy. The Food and Agriculture Organization (FAO) defines policy as the stated objectives that a government seeks to achieve and sustain a decision or a set of decisions made by individuals, organizations, or governments that are oriented toward addressing a topic or issue such as AMR (FAO, 2016).

Key types of policy reviewed include, drafted and approved NAPs; food and animal production policy including animal husbandry regulation; and pharmaceutical legislation. This analysis relied primarily on official government publications, open access legal databases, and collections of legal documents published by international organizations including FAO's legal and policy database (FAOLEX, 2017). In some cases, national AMR policy experts and ministry staff assisted in identifying and providing access to additional policy documents. In total, over 230 policy documents were reviewed. For a list of key documents reviewed for each country see Appendix 1.

This analysis uses the OIE definition of antimicrobial agents: "a naturally occurring, semi-synthetic or synthetic substance that at *in vivo* concentrations exhibits antimicrobial activity (kills or inhibits the growth of micro-organisms). Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition" (OIE, Terrestrial Animal Health Code, 2010). The inclusion of policies on the development of new antimicrobial drugs is not included because this is not a key recommendation nor is it feasible for most low and middle income countries (World Bank, 2016).

Limitations of this analysis include lack of information on how or if the policy has been implemented, enforced or its effectiveness. Second, this paper focuses on animals and agriculture and does not include information on policy related to use and AMR in humans. Third, many policies were translated from the official language to English. Translation of complicated legal language can result in misinterpretation and missing information. Significant effort was taken to ensure the author's understanding of the translation was accurate and consistent with the original text.

POLICY REVIEW

Governance

Governance is at the core of national efforts to reduce or eliminate AMR (FAO, 2016; World Bank, 2016). Recommendations from AMR guidance documents for improving AMR governance include developing a NAP, establishing mechanisms to address AMR, implementing multi-sectoral coordination, and strengthening policy. Examples of mechanisms to address AMR include working groups, delegating specific missions to ministries or other national-level bodies to manage AMR and antibiotic issues and others. Table 4-1 lists three subdomains and details the specific criteria used to assess the policies analyzed under the Governance policy domain.

Table 4-1. Governance Practices and Mechanism(s) to Address AMR and AMU in Food and Agriculture

Policy Subdomain	Criteria
National Action Plans	• Has the government approved an AMR National Action Plan? o If yes, is this plan published with open access? o If yes, does the NAP align with the objectives described in the Global Action Plan?
Mechanism to Address AMR	• Have mechanisms been established to coordinate multi-disciplinary efforts to address AMR at the national level across sectors and agencies? o If yes, how formularized are the relationships between sectors in relation to tactics to address AMR? (i.e. mutual aid agreements, MOU's, informal agreements, inter-ministerial declarations, etc.) • Is there a ministry office or department with an explicit mission to address AMR and AMU in animals and agriculture?
Regulation of Antimicrobials	• Does policy define procedures to control the quality and standards of veterinary medicines? o If yes, do these procedures prohibit the use and distribution of counterfeit or substandard antibiotics? • Is a definition given for veterinary medicines, particularly antimicrobials for use in animals and agriculture? • What measures has the government taken to eliminate, reduce or restrict the nontherapeutic use of antimicrobials in animals and agriculture? • Does policy prohibit or restrict the use of critically important antimicrobials in animals?

	• Does policy address the use of antimicrobials in animal feed?
	  o Does policy establish standards to ensure the safety and quality of antimicrobials in animal feed? (i.e. testing requirements?)
	  o Does policy prohibit or limit antimicrobials in animal feed?
	• Are there standards for advertising antimicrobials for use in animals?
	• Are there labeling requirements for antimicrobials for use in animals?
	• Is a prescription required for antimicrobial use in animals?
	  o If yes, does policy describe who can administer prescription(s)?
	• Does policy regulate:
	  o Who can administer antimicrobials to animals?
	  o Who can sell antimicrobials for use in animals?
	  o Where antimicrobials can be sold for use in animals? (business retailers, pharmacies, etc.)
	• Does policy address the environmental dimension of AMR?
	• Do national policies to address AMR include stakeholders from the environmental sector? (i.e. ministry of environment)

National Action Plans

Viet Nam was the first of the countries reviewed to officially endorse a NAP. In 2013, the Vietnamese Ministry of Health released the National Action Plan on Combatting Drug Resistance (2013 – 2020). Cambodia has three key guidance documents promoting action to address AMR. In 2014, Cambodia released its National Action Plan to Reduce the Threat of AMR Related to Agriculture, Fisheries, Food and Livestock Production (2016 – 2020). Although this NAP is endorsed at the ministerial level it is not technically binding law. The second national document for AMR in Cambodia is the National Strategy to Combat Antimicrobial Resistance (2015 – 2017). Additionally, the One Health Roadmap on AMR (2017 – 2021) has been drafted to guide multi-sectoral action. In Indonesia, the NAP is under development with the goal of submission to the World Health Assembly in May 2017. Laos is developing its NAP and held its first stakeholder meeting to begin the drafting process in November 2016. Laos's NAP is a joint effort by the Ministry of Health and the Ministry of Agriculture and Forestry. As of May 2017, an AMR NAP has not been officially endorsed by a ministry or the government of Myanmar. However, ministerial staff indicate that this plan is being drafted.

Existing NAPs are strongly influenced by the GAP and broadly address the five objectives described in this guidance document. However, the language used to describe these objectives are somewhat different for each country. For example, Viet Nam's NAP includes the following objectives: (1) to raise awareness of community and health workers on drug resistance; (2) to strengthen and improve national surveillance systems on the use of antibiotics and drug resistance; (3) to ensure adequate supply of quality medicines to meet the needs of people; (4) to promote proper safe use of drugs; (5) to promote infection control; (6) to promote proper safe antibiotic use in livestock, poultry, aquaculture and cultivation. In Cambodia, the objectives included in the national strategy were informed by the GAP and modified to fit the national context. Cambodia's NAP focuses on the following objectives (1) strengthening laboratory capacity and AMR surveillance; (2) ensuring uninterrupted access of essential medicines of assured quality; (3) regulating and promoting rational use of medicines; (4) enhancing infection prevention and control; and (5) fostering innovation and research and development of new tools.

It is interesting to note that regionally there is coordination between countries to address AMR. One example of this coordination includes the development of the Association of Southeast Asian Nations (ASEAN) Regional Action Plan on AMR finalized in July 2016. Additionally, through the tripartite collaboration, WHO, OIE and FAO have held regional workshops to assist countries with preparing and refining their NAPs (WHO, 2017).

Governance Coordination to Address AMR

Multi-sectoral Coordination

Coordination across sectors is essential for effective national response and control of AMR (Årdal et al., 2015; Nweneka et al., 2009). Policy support for inter-sectoral coordination and the formality of this coordination differs across the countries. All countries reviewed have established a national multi-sectoral steering committee or working group for addressing AMR or are in the process of finalizing these committees. Most committees were established with the mandate to create and implement the NAP. For example, Cambodia's AMR Working Group was established in 2012 and serves as the main coordinating entity for AMR activities at the national level. This working group is coordinated by the Ministry of Health and is mandated by the

National Policy to Combat AMR to include representatives from different sectors. Viet Nam provides examples of policy support for multi-sectoral collaboration with the recent implementation of several decrees and circulars to support coordination between sectors (Strengthening Capacity for the Implementation of One Health in Viet Nam, 2015; Inter-Ministerial Circular No. 16/2013/TTLT-BYT-BNN&PTNT, 2013). In 2014, Viet Nam's Ministry of Health, Ministry of Agriculture and Rural Development, Ministry of Trade and Industry and Ministry of Natural Resources and Environment and other development partners signed an aide-memorandum to coordinate and jointly implement the NAP across sectors.

Delegation of Authority to Address AMR

NAPs are typically the only policy document that explicitly delegate authority to a ministry or department to address AMR and AMU in agriculture and animals. This is problematic, as NAPs are typically not binding law. In Cambodia's National Action Plan to Reduce the Threat of AMR, the Ministry of Agriculture, Forestry, and Fisheries (MAFF) is directed to implement activities that address AMR and AMU in the livestock and agriculture sector. In Viet Nam, the Ministry of Agriculture and Rural Development has been assigned to address specific aspects of AMR in animals and agriculture including developing regulations on the use of antimicrobials in animals. In Laos, Myanmar and Indonesia, no policy has been identified that mandates or designates a specific office to address AMR. However, legislation in these countries mandates that ministries address disease prevention in animals. A good example of this delegation comes from Laos. Laotian law states that the Ministry of Agriculture and Forestry has the authority to issue regulations for veterinary services, animal health, and prevention and control of epidemic diseases. In addition, the law designates the Livestock and Veterinary Management Authority to manage a list of animal diseases, and regulate activities to prevent and control these diseases.

Regulation of Antimicrobials

Review of policies related to the regulation of antimicrobials described eight topics: (1) quality standards; (2) nontherapeutic use; (3) animal feed; (4) rational use; (5) use of critically important antimicrobials; (6) prescription requirements; (7) authorized retailers; and (8) advertising and labeling standards.

Quality standards

Quality standards help to eliminate or reduce use of substandard antimicrobials. There is no standard definition of poor quality medicines however, WHO uses the SSFFC acronym to describe "substandard/spurious/falsely-labelled/falsified/counterfeit medical products" (WHO, 2012). Research is currently limited linking low quality drugs directly to AMR. However, researchers have demonstrated that certain sub-standard drugs can promote AMR (Leslie et a l., 2009). For instance, poorly manufactured drugs may dissolve incorrectly in the gastro-intestinal tract and influence the amount and rate at which the active ingredient is released into the bloodstream. This is known to promote the development or replication of resistant pathogens (Lesile et al., 2009).

All countries reviewed have policies and standards on the production, importation and exportation of veterinary medicines. Most policies require veterinary drugs to be registered with a designated authority (Viet Nam 2015 Law on Animal Health; Cambodia Law on Animal Health and Production and Joint Prakas No. 363; Myanmar Animal Health and Development Law, Lao Law on Drugs and Medical Products). All countries have standards that must be followed for veterinary drugs to be registered. Additionally, all countries have procedures to control the quality of veterinary medicines. These procedures are typically set by ministries of agriculture. Quality standards regarding the distribution of veterinary pharmaceuticals are important for reducing manufacturing and use of counterfeit and substandard drugs. Countries such as Laos, often describe in policy that their safety requirements are based on international standards and recommendations. Departments or divisions within a ministry are usually directed to monitor and inspect veterinary medicines. For example, Cambodian law designates the MAFF to investigate, regulate, inspect, and monitor all transactions related to veterinary medicines. In Indonesia, veterinary drug inspectors at the district and provincial livestock service offices carry out control and inspections related to veterinary drugs.

A few countries have stand-alone regulations ensuring quality manufacturing of veterinary drugs. In Indonesia, guidelines for good manufacturing practices (GMP) for veterinary medicines were introduced in 1999 (Decree of MOA no. 466, 1999). Viet Nam and Laos both prohibit the use and distribution of fake or counterfeit veterinary pharmaceuticals. Cambodia does not explicitly prohibit fake or counterfeit products, but does ban the use of prohibited substances that are harmful to animals and humans. All countries reviewed provide a definition of veterinary pharmaceuticals in legislation. In Myanmar, the definition includes both veterinary and human pharmaceuticals. However, most laws governing the use of pharmaceuticals in animals and agriculture do not explicitly mention or define antimicrobials.

Nontherapeutic use of antimicrobials in animals

Countries have limited policy regulating the nontherapeutic use of antimicrobials in animals. Most countries do not have legislation that specifically bans the use of antimicrobials for growth promotion or disease prevention. Viet Nam and Cambodia have proposed bans on specific nontherapeutic use of antimicrobials in national strategies to address AMR (Viet Nam's Integrated One Health Action Strategic Plan; Cambodia National Strategy to Combat Antimicrobial Resistance). Viet Nam banned and restricted certain antibiotics for use in animals and agriculture. However, in Viet Nam no specific guidelines are given for the nontherapeutic use of antibiotics in animals. Viet Nam plans to implement, by 2020, a ban on the use of antimicrobial agents for growth promotion in livestock. Further, Viet Nam plans to ban prophylactic treatment of young chickens with colistin (Viet Nam's Integrated One Health Action Strategic Plan). Cambodia's National Strategy to Combat AMR, describes a ban on the nontherapeutic use of antibiotics in food animals and restrictions are proposed to limit the use in animals of critically important antimicrobials for human health. These proposals are expected to be implemented in 2017 by Cambodia's MAFF. Indonesia has banned the use of certain drugs including chloramphenicol and hormone growth promoters in all food producing animals (Decree no. 806, Veterinary Drugs Classifications from the Minister of Agriculture, 1994). No policy regarding nontherapeutic use of antimicrobials were identified in Laos or Myanmar.

Antimicrobials in animal feed

Policies to ensure quality standards for the distribution and use of animal feed exist in all countries. However, such policies are often limited in scope. All countries have a definition on what constitutes animal feed and have set requirements for maintaining quality standards. Most countries also require animal feed to be tested to ensure safety. For instance, a law in Myanmar defines animal feed and stipulates that animal feed must be inspected. In addition, animal feed retailers must obtain certificates requiring animal feed be tested for harmful pathogens and toxins. In Cambodia, there is no provision specifically addressing the use or sale of medicated feed. Under Cambodian law, however, it is illegal to use animal feed that contains prohibited substances including harmful or fraudulent substances, abnormal animal growth substances, or prohibited genetically modified organisms harmful to humans and animals (Law on Animal Health and Production). Similar policy exists in Laos, where the law requires animal feed producers to comply with technical standards relating to production premises, feed production systems, and quality control of feed.

Some countries have policies that ban the use of certain antibiotics in animal feed. For instance, Viet Nam has banned eighteen different kinds of antibiotics for use in animal feed. However, certain antibiotics may legally be added to feed for food animals, for both prophylaxis and growth promotion and some of these antibiotics are critically important for human medicine (Circular 28/2014 / TT-BNN; Clause 1, Article 3 of Decree 08/2010/ND-CP). There are some inconsistencies in Viet Nam on the types of antibiotics that can be used in animal feed, and what types can be directly administered to animals. Twelve types of antibiotics have been banned for direct administration to animals, including bacitracin zinc in Viet Nam. However, bacitracin zinc can be added to animal feed for use in chickens and pigs (Circular No. 03/2012 / TT-BNN; Decree 08/2010/ND-CP). Indonesian law prohibits mixing chloramphenicol, tetracycline, and any hormone growth promoter with animal food. Additionally, Indonesian law explicitly prohibits mixing antibiotic additives in animal food (Law No. 18 of 2009 Concerning Husbandry and Animal Health). For more information on specific legislation to regulate animal feed and the implementing agency, see Table 4-2.

Table 4-2. Regulation of antimicrobial use in animal feed and implementing agency by country

Country	Regulation of antimicrobial use in animal feed	Implementing Agency
Indonesia	• Law No. 65 • CAC/RCP 38-1993 • Law No. 18 of 2009 Concerning Husbandry and Animal Health	Ministry of Agriculture
Cambodia	• Law on Animal Health and Production, 2016; • Prakas on Procedures for Permits Issuance and Technical Standards for Importing, Exporting, Mixing, Repackaging, Stocking, Distributing, Doing Wholesales and Retails of All Kinds of Veterinary Medicines and Veterinary Biologicals; • Prakas on Procedures for the Management of Commercial Veterinary Medicines and Veterinary Biologicals and Mixing of Veterinary Medicines.	Ministry of Agriculture, Forestry and Fisheries
Viet Nam	• Circular 28/2014 / TT-BNN • Decree 08/2010/ND-CP • Circular No. 03/2012 / TT-BNN • Decree 08/2010/ND-CP • Decree on Animal Feed • Terrestrial Animal Health Code • 2015 Law on Animal Health	Department of Livestock; Ministry of Agriculture and Rural Development
Laos	• Law on Livestock Production and Veterinary Matters • Technical Norms on Livestock and Livestock Production Management	Agriculture and Forestry Sector; Ministry of Agriculture and Forestry
Myanmar	• Animal Health and Development Law	Livestock Breeding and Veterinary Department, Ministry of Agriculture and Irrigation

Rational use of antimicrobials

This review identified policies that encourage rational use, create stewardship programs, or discouraged the excessive sale and misuse of antibiotics. Policy in most countries does not explicitly describe or mandate promotion of the rational use of antimicrobials in animals. In Viet Nam and Laos, law specifically states that drugs must be used in accordance with the manufacturer's instructions. Laws also require medicines be taken in compliance with the objectives of the prescription (Law on Drugs and Medical Products; Animal Health Law; Circular No. 50/2009 / TT-BNN and Circular 50/2010 / TTBNN). The law specifically states that pharmacists and businesses are prohibited from promoting misuse or overselling medicines (Law on Drugs & Medical Products). In Indonesia, codes of practice were created to promote the prudent use of veterinary drugs. These codes are harmonized with the Code of Practice for Control of the Use of Veterinary Drugs (CAC/RCP 38-1993). The Code includes guidelines on the use of veterinary drugs in animal feed, and the use of veterinary drugs by authorized companies, institutions or personnel. In Viet Nam and Cambodia, activities to promote antimicrobial stewardship in animal food production are also described in each country's NAP.

Use of critically important antimicrobials

Critically important antimicrobials in human health are drugs that are critical for treating diseases in humans (WHO, 2011). WHO states that "improved management of the use of antimicrobials in food animals, particularly reducing those critically important for human medicine, is an important step towards preserving the benefits of antimicrobials for people" (WHO, 2017). Countries have few policies designed to prohibit or restrict the use of critically important antimicrobials in animals and agriculture. Viet Nam, Cambodia, and Indonesia have legislation that prohibits use of veterinary drugs in animals if that drug demonstrates harm in humans. However, this legislation lacks a definition on what is considered harmful to human health, despite frequent use of the term. More importantly, none of the laws use the term "critically important antimicrobials." Vietnamese law states that "upon detection of veterinary drugs harmful to humans, animals and the environment" the drug in question can no longer be used, and the harmful effects must be "immediately report[ed] to the commune-level People's Committees or the local veterinary specialized agency" (2015 Animal Health Law).

Viet Nam also has legislation that limits the use of certain antibiotics. However, not all antibiotics classified as critically important for use in humans are banned for use in animals in Viet Nam (Circular No. 15/2009 / TT-BNN; Circular No. 29/2009 / TT-BNN; Circular No. 20/2010 / TT-BNN). Cambodian law offers a similar prohibition on drugs that harm humans. The law states that if any component for compounding veterinary medicine is harmful to human health, the certificate of registration for such medicine can be revoked. However, the law does not define what is considered harmful to humans and does not mention antimicrobial resistance. Indonesia has legislation that prohibits the use of animal medicines in livestock that are meant for consumption by humans (Law No. 18 of 2009 Concerning Husbandry and Animal Health). Any person that administers medicine to an animal intended for human consumption will be subject to imprisonment for at least 3 months and is required to pay a fine (Article 90, 2009 Law Concerning Husbandry and Animal Health). Myanmar and Laos currently have no legislation or regulation restricting the use of critically important antimicrobials in animals and agriculture.

Prescription requirements for antimicrobial use

Policies on prescription requirements for antimicrobial use in animals are quite varied between countries. In Viet Nam, Myanmar, Indonesia and Laos, policy describes that pharmaceutical drugs for use in animals must be administered with a prescription. In Myanmar and Laos, legislation on prescription requirements for pharmaceuticals encompass both animal and human drugs. For instance, in Myanmar's National Drug Law states that prescription drugs must not be sold to anyone except by written prescription from a registered physician, dental surgeon or veterinary surgeon. In Indonesia and Viet Nam, veterinary pharmaceuticals may only be obtained with a veterinarian's prescription. Viet Nam and Indonesia stipulate specific conditions that veterinary practitioners must meet to practice veterinary medicine. In Cambodia, there is no law specifically stating that a prescription is required for antibiotic use in animals. Cambodian law directs the MAFF to “regulate trade, production, mixture, prescription and the usage of veterinary medicines, veterinary biologicals, and veterinary materials” (Cambodia Law on Animal Health and Production). Countries provide very limited regulation about who is legally allowed to administer drugs to animals. Only Indonesia regulates who may legally administer drugs to animals. Indonesian law requires veterinary medicines be used only under the supervision of a veterinarian or member of the Animal Health Force (Law No. 18 of 2009 Concerning Husbandry and Animal Health). No guidelines were identified in any of the countries reviewed that describe the relationship between farmers and veterinarians and prescription requirements

Authorized retailers of antimicrobials

Most countries have very specific policy delineating requirements for veterinarians, pharmacies or businesses seeking to sell animal pharmaceuticals. Most policy mandates that pharmacies or other medical businesses must first register with a designated agency prior to making any sales. The registration process is varied, but typically consists of proof of national identity and credentials. Limited regulation and guidance is given on whether a licensed pharmacist or veterinarian is required for businesses to sell drugs. Some countries, such as Viet Nam, have specific training requirements for pharmacists or drug-retailers before they may sell antimicrobials for use in animals. Similarly, Cambodian regulation requires any institution selling veterinary medicines to have a license. In Cambodia, only veterinarians can apply for a license from the Ministry of Agriculture, Forestry, and Fisheries to sell veterinary medicines (Joint Prakas No. 363). In addition, Cambodia prohibits veterinarians from directly selling animal pharmaceuticals—including antibiotics—to farmers, unless they have a specific permit issued by MAFF.

Myanmar has limited policy on who can sell veterinary pharmaceuticals. Myanmar's National Drug Law states that a business can sell pharmaceuticals as long they apply for and are granted a drug retailer's license. In Indonesia, any business manufacturing, preparing, or circulating animal medicine must have a business license (Law No. 18 of 2009, Concerning Husbandry and Animal Health). Other Indonesian laws stipulate that drug retailers must have a part-time veterinarian, pharmacist, or a full-time assistant pharmacist, as the person-in-charge (Law on Hard Drugs, 1949). In Laos, law outlines provisions on who can sell antimicrobials and stipulates that the sale of drugs and medical products be conducted by authorized retail pharmacies only. Policies regulating where veterinary pharmaceuticals can be sold is weak. In Viet Nam, requirements for where veterinary pharmaceuticals can be sold are limited to quality standards for the physical premise. Similar requirements exist in Laos, Myanmar and Cambodia. In Indonesia, antibiotics for use in animals can be sold in 'depot distributors of veterinary drugs or pet shops' (Minister of Agriculture Decree No. 806/Kpts/TN.260/12/94). Requirements are described for depot distributors including licensing requirements standards for cleanliness.

Advertising and labeling

Regulation on advertising veterinary pharmaceuticals is similar among countries. In Viet Nam, regulation prohibits advertising prescription drugs, including antibiotics, to the public in any form (Law on Pharmacy, 2005). Cambodia, Laos, Myanmar and Indonesia require drugs be registered and comply with specific requirements before being advertised. In Cambodia, advertisers of veterinary pharmaceuticals must comply with mandates from the Animal Health and Production Unit under the MAFF (Law on Animal Health and Production). Myanmar's National Drug Law, allows registered drugs to be advertised that comply with very specific requirements. Further, drugs that require a prescription can only be advertised to doctors, dental surgeons, veterinary surgeons, nurses, pharmacists, and paramedics. Indonesia requires that all advertising materials be submitted to the Indonesian National Agency of Drug and Food Control

(NADFC) for approval prior to advertising. Laotian law prohibits unapproved drugs being advertised and it is illegal for advertisements to make any misleading claims for approved drugs (Drugs and Medical Product Law).

All countries have labeling requirements of veterinary pharmaceuticals. However, label requirements differ greatly. For most countries, requirements are described in national pharmaceutical and drug laws. All countries have minimum standards that the label be written in the native language, state the active ingredient, comply with registration requirements, and provide instructions for use (Cambodia 2015 Law on Animal Health; Myanmar National Drug Law; Viet Nam 2015 Law on Animal Health; Laos Drugs and Medical Product Law; Indonesia Government Regulation No. 78). In Myanmar, Viet Nam and Indonesia, drugs used for veterinary purposes must state "for animal use only" on the label. Viet Nam has legislation that requires that "the withdrawal/withholding time for each animal species to be treated" be clearly stated on the label of antibiotics used in animals (Circular No. 03/2009). Withdrawal time is the time that the antibiotic should stop being used to clear the animal's system before the animal is slaughtered, to ensure products from that animal are free from unsafe antibiotic residues. Laotian law requires that drugs carry a seal of approval from the Laos Food and Drug Department to help distinguish unregistered drugs.

The environment

Increased use of antimicrobials in animal husbandry is a significant concern for potential spread of AMR and antimicrobial residues to the environment and to humans (Hershberger et al., 2004; Speksnijder et al., 2014). Resistant organisms and antimicrobial residues can spread into the environment in several ways through various animal husbandry practices, and farm and pharmaceutical run-off (Hershberger et al., 2004). Consideration of the relationship between the environment and AMR is very limited in national policies. Viet Nam has made important steps in addressing environment concerns as it relates to AMR. Viet Nam includes the Health

Environmental Management as a commissioner in the Steering Committee for implementing the NAP. Guidelines for controlling the spread of drug-resistant microorganisms in the environment were jointly drafted by Viet Nam's Ministry of Natural Resources and Environment, Ministry of Health, and the Ministry of Agriculture. Viet Nam's Environmental Protection Law requires the Minister of Natural Resources and the Environment to unify each state's environmental protection. Under this law, the Ministry of Natural Resources and Environment issued a list of hazardous wastes and standards for hazardous waste management (Decree 38/2015/ND-CP, Circular 36/2015/TT-BTNMT). This list includes management of hazardous waste related to antibiotics and antibiotic resistance (Circular 36/2015/TT-BTNMT). Cambodia has enacted several policies to help prevent the discharge of harmful substances, including antimicrobials, into the environment (Law on Fisheries; Law on Pesticides and Fertilizers). The Prakas on Medical Waste Management (2009) prohibits antibiotics from being discharged into the public sewer system. The Cambodian Law on Pesticides and Fertilizers prohibits disposal of pesticides on land and into water sources that could be harmful to the environment.

Infection Prevention and Control

Policy specific to biosecurity (e.g. prevention and control of containments) can minimise the spread of pathogens, including those that are resistant. This decreases the likelihood of infection, and thereby reduces the overall need for antimicrobials (FAO, 2017; WHO, 2017; O'Neill, 2016). Effective infection prevention and control is critical for reducing the volume and number of antimicrobials used in animal husbandry and therefore limiting the opportunity for drug resistance strains from developing (O'Neill, 2016). Husbandry factors that contribute to AMR include poor biosecurity measures such as inadequate disinfection and animal housing cleaning. Additional practices that contribute to AMR include practices that promote stress on animals (i.e. transport of animals, stocking density, etc.). Best management practices, and industry standards can be used to set standards that ensure safe and sustainable husbandry practices. When implemented, these standards can minimize the spread of AMR in the environment. Table 4-3. describes the criteria used to assess policies related to infection prevention and control specific to AMR in animals and agriculture.

Table 4-3. Policies related to infection prevention and control and AMR and AMU in animals and agriculture

Policy Subdomain	Criteria
Infection Prevention and Control	• Has the government established infection prevention guidelines for animals and agriculture? • Does policy require infection prevention training specific to AMR for animal health workers, animal food producers (i.e. farmers), veterinarians, or others?

Several NAPs describe infection prevention and control efforts to address AMR in animals and agriculture. For instance, Viet Nam and Cambodia's NAPs describe targets for improving infection prevention and control efforts, including enhancing farm biosecurity measures and promoting good animal husbandry practices. Activities described in Cambodia's NAP, include increasing vaccination coverage, promoting biosecurity measures at the farm level, strengthening the control of animal movement and enforcing existing legislation on disease management. The Cambodian NAP describes activities for AMU and AMR training for village animal health workers. Viet Nam's NAP calls for conducting trainings for health workers on AMR treatment guidelines. In its NAP, Viet Nam also aspires to "gradually improve the system of legal documents and instructions on technical expertise in infectious disease control, infection control, surveillance of drug resistance and enhancing rational drug use" (Viet Nam, NAP on Combatting Drug Resistance, 2013).

Several countries have policy guidelines on infection prevention and control but these are not specific to preventing AMR. For instance, Indonesian policy has guidelines for eradicating animal diseases and for improving infection prevention and control at the farm level (2009 Law on Husbandry and Animal Health). Under this law, efforts to control and prevent animal diseases include observation, identification, prevention, safeguarding, eradication, and/or medication.

However, this law does not provide specifications on antibiotic use nor does not it mention AMR. In Laos, livestock and veterinary guidelines exist for the prevention and management of animal diseases. These regulations do not however, mention AMR or AMU (Decree on the Control of the Movement of Animal and Animal Products and the Technical Norms on Livestock and Livestock Production). Laos's Decree on the Prevention and Control of Animal Diseases provides the principles, regulations, processes, and methods for preventing and controlling animal diseases. The Technical Norms on Livestock and Livestock Production Management provide very specific disease management guidelines for animal diseases. Viet Nam's veterinary law provides guidelines on disease prevention, quarantine of animals and animal products, slaughter control, and veterinary hygiene. In Cambodia, the 2016 Law on Animal Health and Production establishes specific standards for controlling and preventing the spread of animal diseases. This law describes guidelines on the management of animal health and production at a national level. Myanmar has similar regulations regarding disease inspection requirements, and certifications for disease free animals (Animal Health and Development Law).

Awareness

Awareness raising campaigns and education programs are key ways for countries to increase knowledge and understanding of AMR among stakeholders. The GAP recommends that countries take immediate steps to raise AMR awareness and promote behavior change among stakeholders. Further, FAO recommends that countries customize advocacy campaigns to target different stakeholders and present key messages that fit national contexts (FAO Action Plan on AMR, 2016). Recommended awareness raising activities include campaigns that use mass media to target the general public, and initiatives to improve educational curriculum in both academic and non-academic settings.

Table 4-4. Policy to Support Awareness and Education on Antimicrobial Resistance

Policy Subdomain	**Criteria**

Awareness	• Has the government established policy to increase national awareness of AMR among the general public?
	  o If yes, does this include participation in an annual world or regional AMR awareness campaign?
	• Has the government established policy that supports inclusion of AMR and related topics in:
	  o Undergraduate and graduate curricula such as veterinary medicine?
	  o Continuing education programs focused on veterinary, livestock and agricultural training?

Most National Action Plans (NAPs) promote AMR awareness raising activities. Viet Nam's NAP attempts to increase AMR awareness through mass campaigns targeting the general population, human healthcare professionals, and students. Additionally, the NAP recommends developing AMR curriculum for tertiary institutes and universities, providing AMR training to increase the capacity of clinical microbiology laboratories, and drug resistance prevention training programs through collaborations between domestic and foreign institutions. Cambodia's NAP focuses on improving AMR training and education in undergraduate and graduate curriculum, as well as activities that target the general public through a mass media campaign. Cambodia's National Strategy to Combat AMR, endorses plans to conduct seminars on AMR for human, animal and other related health professions.

Although official participation in global AMR events is increasing, this participation is not recommended in policy or a national strategy document. Cambodia and Indonesia participated in World Antibiotic Awareness Week (WAAW) in 2016. This event included mass media events and activities. Laos participated in its first WAAW in 2015 and again in 2016, where it held its first multi-stakeholder workshop on AMR. Four ministries from Viet Nam participated in WAAW in 2015 and 2016. In 2016 events at the WAAW included a mass media campaign in the capital city that gathered pledges for responsible antibiotic use. A lecture series, targeting students and professionals, was also held at different locations around the country (WHO, 2016).

Evidence

Documenting resistance through surveillance, monitoring, and research provides essential information for improving national responses to AMR. Evidence is critical for improving knowledge, informing appropriate prevention practices, and promoting the rational use of antibiotics. Countries can improve the evidence base by establishing policy that supports surveillance and monitoring systems for AMR and AMU. Scholarship recommends gathering two types of data to improve AMR/AMU evidence bases: (1) monitoring the number of AMR infections (isolates from AMR infected animals); and (2) monitoring antimicrobial consumption at the farm level (O'Neill, 2016).

Policy should facilitate AMR research, beyond routine surveillance and monitoring activities. Research is important for improving knowledge and establishing evidence based policies. Priority research topics on AMR and AMU have been identified by WHO and FAO. Research topics range from interspecies transfer of AMR through humans, to agriculture and the food production environment, to understanding AMU and its impact on the farm environment (FAO Action Plan on AMR, 2016; WHO, 2016).

Table 4-5. Policy Support for Building the Antimicrobial Resistance and Use Evidence Base

Policy Subdomain	Criteria
Evidence	• Has the government established policy to support the development and implementation of a national surveillance and monitoring system for AMR and AMU? • Has the government established policy to support research on AMR outside of surveillance and monitoring activities? • Does national policy include support for building or maintaining national laboratory capacity to identify antimicrobial resistant bacteria?

There are currently no nationwide AMR surveillance or monitoring systems for animals among the countries reviewed. National Action Plans (NAPs) in Viet Nam and Cambodia endorse plans for establishing a surveillance system and developing a database on AMR and AMU in humans and animals. While countries do not have any national level surveillance programs established yet, many have specific research groups or academic institutions that analyse drug resistance trends. Surveillance and monitoring activities have occurred in some countries. In Indonesia, a preliminary study was conducted in 2012 to monitor antimicrobial resistance in sentinel bacterial isolated from poultry meat from one area in West Java. In 2012, the program was continued and expanded to all of Java Island and is ongoing. An initial pilot program to monitor AMR ran from 2012 to 2013. However, it is recognized as a national-level program to monitor antimicrobial resistance in indicator bacteria (*E. coli* and *Salmonella spp*.) (Nhung et al., 2016).

Laboratory and human capacity to identify resistant bacteria are very limited in most countries. Many countries recommend strengthening laboratory capacity to detect AMR in NAPs. Viet Nam and Cambodia propose similar activities to improve laboratory capacity, including building laboratories and reference laboratories, improving standard test procedures, and creating guidelines for clinical microbiology laboratories. Viet Nam developed an AMR reference laboratory for antimicrobial stewardship (One Health Strategic Plan, 2016). Viet Nam has also set the goal to build a network of thirty laboratories across the country for detection of AMR. In Myanmar, two central veterinary diagnostic laboratories and four regional veterinary diagnostic laboratories exist. Indonesia has eight laboratories that test for animal diseases. These laboratories also have the capacity to test for veterinary drug residues and microbial containments. Indonesia also has Veterinary Public Health Laboratories located in districts and provinces, which can conduct simple tests of livestock products.

Limited AMR research has been conducted in the countries reviewed. Viet Nam describes activities to promote scientific research on AMR in their NAP. Viet Nam's NAP describes several research priorities: monitoring the circulation of counterfeit drugs in the market, developing evaluation indicators, and establishing a system for collecting and processing information. Viet Nam's Integrated One Health Strategic Plan creates strategies for research on environmental and food reservoirs of AMR organisms.

Each country has policies that direct agencies to conduct research on various topics related to animal diseases and animal husbandry. For instance, in Indonesia, the Government and regional Governments are obligated to conduct research on animal diseases and development of husbandry and animal health (The Husbandry and Animal Health Law No. 18 of 2009). Other countries have legislation that mandates agencies to establish surveillance systems for different animal diseases of concern. For instance, Laos's Decree on the Prevention and Control of Animal Disease states that the "Livestock and Veterinary Management Authority at the central level shall establish an appropriate system of surveillance, warning and disease traceability in advance, for listed diseases" (Article 8).

DISCUSSION

Findings from this analysis demonstrate that countries have policies and governance mechanisms to build upon to more effectively address AMR. All countries have already approved or drafted a NAP. These NAPs align with key AMR guidance documents, including the GAP, and provide an important foundation in creating national interventions to address AMR. NAPs provide guidance for establishing awareness initiatives, supporting surveillance and monitoring systems, improving infection prevention and control and promoting rational AMU practices. All countries reviewed have established, or are in the process of establishing, a multi-sectoral steering committee or working group. There are also efforts at the regional level for coordination and collaboration on AMR activities. Countries have enacted pharmaceutical and animal husbandry laws to regulate antimicrobial use in animals and agriculture. Policies to regulate the use of antimicrobials and address responsible marketing, sales, and manufacturing have been enacted. Some countries require prescriptions to use antimicrobials in animals, and most encourage responsible advertising of antibiotics. Several countries prohibit counterfeit drugs and overselling of antimicrobials.

Many countries are also starting to implement bans of specific antibiotics for use in animals and have established policy goals to eliminate or restrict the nontherapeutic use of antimicrobials. NAPs promote awareness raising initiatives focusing on different target populations and countries are increasing their participation in national and global awareness raising events. Policy support for countries to develop surveillance and monitoring systems specific to AMR and AMU were identified in each country. Additionally, countries have policy support for reporting disease occurrences for specific diseases, while other laws mandate the establishment of surveillance systems for specific infectious diseases. NAPs describe infection prevention and control efforts to address AMR in animals and agriculture as well as several countries have already enacted policy guidelines on infection prevention and control.

Critical gaps in AMR policy in this region were identified. Legally binding delegation of duty and/or authority to act on AMR issues are limited. Specific, detailed regulation of the use of antimicrobials is also weak. Countries often lack adequate guidelines for the distribution of antimicrobials. For instance, guidance on who and where antimicrobials can be sold, and who may legally administer antimicrobials is very limited in most countries. Laws regarding who can sell drugs for use in animals and where drugs can be sold are often ambiguous. For example, in Viet Nam, minimal requirements for drugs stores for veterinary pharmaceuticals are described in policy. Vietnamese law states that the Health Minister will specify geographic areas where drug-retailing establishments are allowed. However, the law does not mention important details such as if sales of veterinary pharmaceuticals have separate requirements from human pharmaceuticals. In Cambodia, no specific legal provisions on where antimicrobials can be sold were found. The Cambodian Law on Animal Health and Production states that distributors, wholesalers or retailors of veterinary medicines must be represented by a veterinarian. This law does not mention whether veterinary medicines, including antibiotics, may only be sold in pharmacies or could be sold in other shop types.

Although some countries have established goals to reduce the nontherapeutic use and use of critically important antimicrobials, binding policy is currently minimal and no country has established a reduction target for AMU. As surveillance and monitoring activities progress, informed reduction targets can be established to better understand the impact of interventions and to document national progress.

Most countries do not have legislation that specifically bans the use of antimicrobials for use as growth promoters or for disease prevention. There is also a lack of policies regulating the use of antimicrobials in animal feed. Although policies to ensure quality standards for the distribution and use of animal feed exist in all countries, these policies are often limited in scope. For instance, they do not explicitly mention or describe antimicrobial additives. These limitations in policy may influence the overuse and misuse of antimicrobials in animal productions systems. Evidence from high-income countries demonstrates that curbing nontherapeutic and therapeutic use of antimicrobials can reduce resistance (Agersø et al., 2011; van den Bogaard et al., 2000; Agersø et al., 2013).

Blanket bans or other policy measures to reduce the nontherapeutic use of antimicrobials should be complimented with stakeholder engagement, awareness raising activities and substantial investment in infection prevention and control initiatives. Additionally, bans should be based on scientific recommendations grounded in evidence. When countries are adapting new policy, pilot programs should be used to understand the effectiveness of these policies before full scale implementation. This is particularly true of changes in regulatory policies such as prescription requirements because these are context specific and depend on different factors such as the number of veterinarians in a district or province and farmers access animal healthcare. Such policy interventions are highly context specific compared to other AMR policies, such as surveillance policy that can be a bit more standardized across countries.

Very little AMR focused policy considers the environment. As countries further strengthen their national strategies to address AMR there needs to be greater consideration for the environment. Countries can address environment threats posed by AMR by including environmental regulators in the development and implementation of NAPs. National regulations should be established that require monitoring and controlling the spread of AMR into the environment targeting different exposure pathways. Biosecurity at the farm level can help to reduce the amount of residues spread into the environment. Environmental regulators can also establish national targets for maximum levels of antimicrobials discharged during manufacturing pharmaceutical products. All countries have agencies designated to address environmental issues as they relate to public health. The current duty of these agencies does not appear to include monitoring AMR-related impacts, or to respond such impacts. There is potential for these agencies to oversee the environmental aspects of AMR. For instance, Myanmar has an Environmental Conservation Department under the Ministry of Conservation and Forestry that is charged with carrying out environmental impact assessments and managing environmental pollutants. By delegating a mission or duty this agency could also monitor local environments for additions of antimicrobial residues, and related impacts from AMR.

Regulation for the control of labeling on antimicrobials among the countries reviewed is minimal. Labeling has an important role to play in communicating to the animal producer the what is included in the product particularly animal feed, describing the scarcity of antibiotics and ensuring product registration compliance. Some countries lack policy that explicitly prohibit fake or counterfeit veterinary pharmaceuticals. Updating policy language to prohibit fake or counterfeit products is important for reducing the manufacturing, use and distribution of these products.

An important influencer of AMU policy are standards set by exporting countries. For instance, the EU, Australia and the US have put pressure on seafood exporters to reduce the excessive use of antibiotics used in fish (FAO, 2017). Antibiotic residues accounted for 28% of EU rejections and 20% of US rejections of aquaculture imports (FAO, 2017). Viet Nam, China, Thailand, Bangladesh, and Indonesia have the most frequently rejected aquaculture products (FAO, 2017). In 2012, Australia blocked shipments of fish from Viet Nam after enrofloxacin, an antibiotic banned in Australia was detected (Phys.org, 2012). Recently, both Japan and the EU have imposed temporary bans on Vietnamese fish and seafood due to illegal drug residues. Some foreign animal manufacturers are changing their antibiotic use in fish as a result of these bans however information on specific regulation changes were not identified (Tuoitre News, 2016). In April 2017 the US Food and Drug Administration (FDA) issued an import alert that its district offices could detain and test all imports of shrimp and prawns from Malaysia (Bloomberg, 2016). Fish products from different Southeast Asian countries are often exported through Malaysia (FAO, 2017). Malaysia's Ministry of Health responded by announcing that it would tighten controls at processing plants and assume the authority to issue certificates of origin from chambers of commerce (Bloomberg, 2016).

Policies to address infection prevention and control are varied. Increased support to improve animal health should be considered by all countries with a focus on herd health and herd immunization programs, promoting and enforcing agricultural best management practices, and enforcing biosecurity standards. These policies will in turn reduce the need for antimicrobial use in animals and agriculture. Guidelines for infection prevention and control should be adapted for each country context and consider local farming systems. Additionally, a focus should be given to animal health workers and farmers for infection prevention and control training. The Dutch government has made substantial investments in infection prevention and control efforts at the farm level. One measure created for improving infection prevention and control is the Farm Health Plan (FHP) established by the Dutch Taskforce Antibiotic Resistance in Animal Husbandry. The FHP requires farms to work with their veterinarian to develop a plan that identifies farm-specific risk factors for infectious diseases and designs specific management measures to control and prevent these diseases. This measure along with other regulatory and policy actions have been credited with contributing to a 56% nationwide reduction in antimicrobial use in farm animals from 2007 – 2012 (Speksnijder et al., 2014).

Finally, no AMR or AMU surveillance or monitoring systems exist in any of the countries included in this review. Efforts are currently underway in countries to assess current laboratory capacity for AMR surveillance and plans for developing these systems are included in NAPs. Surveillance systems are critical for building the evidence base and informing AMR programs and interventions. Surveillance is also paramount in detecting and responding to disease outbreaks. Most high-income countries have developed surveillance systems on AMR and for some countries, such as Japan, this information is used to inform risk management practices for antimicrobial use in animals. Japan uses information gathered from the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) to regulate what antimicrobials can be added to animal feed. Japan relies on the following risk management measures, informed by international standards, to control what substances are added to animal feed: (1) substances which pose risk to human health are not designated as antibiotic feed additives; (2) specifying applicable animal species, breeding stages (products for lactation period, for fattening period, etc.); and (3) standard amounts to be added in feed. In addition, Japan conducts an annual national survey under the framework of JVARM, to identify trends in AMR and to evaluate the effectiveness of each risk management measure (Japan Ministry of Forestry and Fisheries, 2017).

Common gaps in AMR education and awareness policy include limited coordination between sectors. Coordination between ministries of agriculture and education could improve AMR education in undergraduate and graduate curricula, and could also improve continuing education programs focused on veterinary, livestock, and agricultural professionals. Further, NAPs typically have limited or no specific details about AMR awareness raising activities or training programs. Most activities on awareness described in NAPs focus on annual campaigns and do not typically describe ongoing efforts. Awareness raising campaigns have received widespread support; however, there is limited evidence to support their effectiveness to raise awareness or impact antimicrobial use (Huttner et al., 2010). Awareness campaigns in Europe implemented between 1997 and 2007 have been associated with a 6.5–28.3% drop in the mean level of antibiotic use in humans (Huttner et al., 2010; Filippini et al., 2013). However, this finding should be interpreted with caution as many other policy initiatives and regulatory activities were implemented during this time period.

Although research documenting the implementation of policies in the countries reviewed is limited, and beyond the scope of this review, there is some evidence to demonstrate that there is a significant gap in the implementation and enforcement of existing policy. For countries that have already banned certain antibiotics for use in animals and agriculture the extent to which these policies have been implemented is questionable. For instance, in Viet Nam, a 2013 study found that at least 45 antibiotics some of which have been banned (e.g. chloramphenicol) were commonly used by farmers and veterinarians for nontherapeutic purposes (Kim et al., 2013). Additionally, a 2016 study in Viet Nam found that 58 out of 1,893 animal feed production plants inspected, were found to be using banned substances with banned substances identified in 17 out of 1,239 animal feed samples and 257 out of 3,972 pigs (AsiaNews, 2016). Research on illegal distribution of antimicrobials in animals is limited however we can borrow from examples on human use. In some countries that require prescriptions for antibiotic drugs these drugs can still be easily purchased over the counter. In Viet Nam for instance, a 2010 study determined that 88% of antibiotics were sold without a prescription in urban pharmacies and 91% in rural pharmacies (Thuy Nga et al., 2014). A 2016 survey conducted in Indonesia found that 85% of pharmacies in Jakarta sell drugs without prescription (Asia News, 2016). All countries reviewed require that drugs be registered with the designated authority before use in animals and humans. However, estimates suggest that Laos has about 2,100 illegal drug retailors and Cambodia has roughly 2800 illegal medicine sellers and 1000 unregistered medicines on the market (Pincock, 2003).

Existing policies can be improved to more effectively prevent or reduce the impacts AMR. One way to improve existing policies is to interpret and/or enforce polices in ways that target the systems and actors that contribute the most to AMR. For example, awareness raising on existing policies can target specific groups such as drug retailors, prescribers and animal producers. Second, existing policies can be improved by enacting amendments that modify language or add enforcement tools that fit the local capacity. Governments can enhance the quality of their policy frameworks by ensuring that language used to describe policy is simple, clear and understandable with definitions included for key terms such as 'misuse', 'harm' or 'overselling'. Further, governments should identify gaps in enforcement practices, develop capacity to fully implement existing and future policy, and undertake awareness raising campaigns on existing policies. In addition to clarifying and strengthening AMU guidelines, measures to make veterinarians accountable for prescribing practices should be considered to promote rational use of antimicrobials. Governments should consider adapting policy that prevents pharmaceutical companies from providing financial incentives to veterinarians for prescribing antibiotics.

CONCLUSION

This analysis demonstrates that countries have policies that can be used and built upon to more effectively address AMR at the national level. Most countries have enacted pharmaceutical and animal husbandry laws to regulate the use of antimicrobials in animals and agriculture. Many countries require prescriptions for use of antimicrobials in animals, and most encourage responsible distribution of antimicrobials through advertising and labeling standards. Several countries prohibit counterfeit drugs and overselling antimicrobials. Many countries are also starting to implement bans of specific antibiotics for use in animals and have established policy goals to eliminate or restrict the nontherapeutic use of antimicrobials. With the development of NAPs to address AMR, countries have the foundation to develop AMR/AMU awareness initiatives, to provide support for surveillance and monitoring systems, and improve infection prevention and control systems.

Common gaps in existing policy across countries included unclear descriptions of the legal use of antimicrobials in animals including weak or nonexistent standards for limiting or reducing the use of critically important and nontherapeutic use of antimicrobials; limited policy support for awareness raising and surveillance activities; and limited formal coordination mechanisms for inter-sectoral coordination between sectors. Most ministries do not have formal AMR coordination mechanisms such as inter-ministerial declarations or memorandums of understanding between sectors or ministries. Establishing formal mechanisms for coordination between sectors to help improve communication and collaboration for multi-sectoral efforts is important. Legislation that specifically bans the use of antimicrobials for use as growth promoters or disease prevention has not been enacted for most countries. It is critical that antimicrobial use for growth promotion or prophylaxis in animals should be reduced or eliminated however these policies should be coupled with adequate investment in improved infection prevention and control in livestock. Additionally, many countries lack an explicit description or mandate to promote the rational use of antimicrobials in animals.

Further research into specific use and distribution of antimicrobials is needed and policy can support and guide these actions by designating authority or mission to departments and setting and prioritizing research agendas. Greater analysis is needed to understand how policies are enforced and the political and economic context of national policy frameworks and to identify gaps in enforcement. As countries adapt their policies and implement NAPs, the local context and capacities must be considered. Countries should strive to use evidence-based solutions; ideally evidence gathered in their own country. To make sure that AMR is a priority, countries need to cultivate political commitment to this issue at the national level. As WHO, FAO and other international organizations call for further national action on AMR, policy-makers may feel pressure to make swift policy decisions to meet international expectations. However, countries should be mindful of their approach when adopting new policies, even when policies have been effective in other settings.

Chapter 5

Antimicrobial Resistance Policy in Asia and the Pacific: Findings from an Exploratory Study

SUMMARY

The objective of this analysis is to better understand national regulatory frameworks designed to address antimicrobial resistance (AMR) and antimicrobial use (AMU) in the food and agriculture sector. Information was obtained during focus group discussions at the 2016 Regional Workshop on AMR in Asia and the Pacific, hosted by the Food and Agriculture Organization (FAO) Animal Production and Health Commission for Asia and the Pacific (APHCA) and the World Organisation for Animal Health (OIE). Twelve countries from South Asia, the Pacific and Southeast Asia contributed: Afghanistan, Bangladesh, Bhutan, Cambodia, India, Indonesia, Myanmar, Nepal, Philippines, Samoa, Sri Lank and Viet Nam. Focus group discussions focused on national policies, including background information about national strategies, local constraints and challenges, and proposed AMR policy.

This study revealed several key findings. Most countries reported existing animal husbandry and veterinary pharmaceutical policy that can be used to address AMR. Respondents described plans for enacting new policies, many of which focus on developing and implementing national action plans. Proposed policies address objectives described in the World Health Organization (WHO) Global Action Plan (GAP) to address AMR, particularly awareness raising activities, and building surveillance and monitoring capacity. Respondents identified several stakeholders that are critical to shaping AMR and AMU policies including veterinary pharmaceutical associations, farmers' associations, and ministries of agriculture. Common gaps and constraints in addressing AMR described by respondents include limitations in infrastructure, and a lack of financial and human resources. This study can be used to shape recommendations for AMR and AMU policy interventions and inform existing and future policy. Findings from this analysis can support countries in allocating finite resources to create a more effective enabling environment to respond to AMR.

INTRODUCTION

Antimicrobial resistance (AMR) poses a significant risk to animal and human public health around the world (WHO, 2016; FAO, 2016). With the growth of global trade and travel, resistant microorganisms can spread very quickly throughout the world leaving no country invulnerable (OECD, 2016). Drug-resistant bacteria are responsible for 25,000 deaths in Europe annually and with resistance levels rising many infectious diseases may one day become untreatable (ECDC, 2009). AMR affects high- and low-income countries alike, however, estimates indicate that AMR will have an "increase in extreme poverty" and will have a disproportionate impact on the economics of low-income countries (World Bank, 2016). Immediate concerns for AMR are similar across low- and middle-income countries. Many of these countries are experiencing increasing rates of drug-resistant tuberculosis (TB), malaria, and HIV/AIDS and threats to livestock and food security (WHO, 2014; Gelband et al., 2014; Archawakulathep et al., 2014). Without effective and timely interventions, AMR associated human mortality is expected to increase from 700,000 global deaths in 2014 to over 10 million by the year 2050 (O'Neill, 2016). In addition to the impact on morbidity and mortality, AMR also causes a substantial economic burden. The U.S. Centers for Disease Control and Prevention (CDC) estimates that in the U.S. alone, the annual impact of antibiotic resistant infections on the economy is $20-35 billion in excess health care costs (CDC, 2013). Economic losses linked to AMR are anticipated to exceed $100 trillion annually by 2050 (World Bank, 2016).

The emergence and spread of AMR is influenced by antimicrobial use in humans and animals including the misuse and overuse of antimicrobials (Hershberger et al., 2004; Speksnijder et al., 2014). Low- and middle-income countries often have limited regulation on antimicrobials including weak drug quality assurance systems creating conditions for the misuse of antimicrobials (Gelband & Delahoy, 2014). In some countries, antibiotics are widely used in healthy food-producing animals for non-therapeutic purposes including promoting growth and preventing disease (Landers et al., 2012). Research suggests that antimicrobial resistant microbes carried by infected animals can transfer to humans and cause disease. Resistant microorganisms carried by food-producing animals can spread to humans through consumption of contaminated food, direct contact with animals, or through environmental vectors like contaminated water (Marshall et al., 2011). In South Africa, *Salmonella enterica*, *Escherichia coli* (E. coli), and *Enterococcus spp*. have been found resistant to sulfonamides and tetracycline in food animals and domestic pets (Mendelson and Matsoso, 2015). The 2016 O'Neill Review on AMR, suggests there is a growing consensus that unnecessary use of antibiotics in animals and agriculture is a significant concern for human health. (O'Neill, 2016).

METHODS

To better understand the policy environment to address AMR and AMU, representatives from twelve countries were asked during focus group discussions to describe their current policy to address AMR and AMU in animals and agriculture. Respondents included representations from ministries of agriculture working on AMR in different capacities. Countries were asked to provide information on the following questions as they relate to AMR and AMU: (1) identify current policy to address AMR and AMU; (2) describe planned policy; (3) identify key institutions for implementing policies; (4) identify key stakeholders in shaping AMR and AMU policy; (5) describe steps to ensure policy compliance; (6) identify determinants of AMR and AMU policy; and (7) describe constraints and challenges to policy compliance. The focus was on AMR and AMU in animals and agriculture however human health policy was also discussed where applicable, including pharmaceutical laws that encompass both animal and human antimicrobial use. Participating countries included Afghanistan, Bangladesh, Bhutan, Cambodia, India, Indonesia, Myanmar, Nepal, Philippines, Samoa, Sri Lank and Viet Nam. This policy information was gathered during the 2016 FAO Animal Production and Health Commission for Asia and the Pacific (APHCA) and OIE Regional Workshop on AMR in Asia and the Pacific funded by the United States Agency for International Development (USAID). By examining country's current and planned policies to address AMR, this analysis contributes to a more comprehensive understanding of countries regulatory frameworks to protect public and animal health from AMR and identifies where gaps still exist.

RESULTS

Current policies

Eleven of the twelve participating countries identified at least one current national policy used to address AMR and AMU. Common components of these policies reported included regulations to limit access to antibiotics including feed supplement acts, drug manufacturing regulation and control, food safety acts, and animal disease acts. Respondents frequently reported that AMR and AMU policies focused on animals and agriculture were limited. Drug and food laws related to human health were frequently reported. For example, Bhutan described seven laws, five of which focused on AMR and AMU in humans. The majority of the policies were enacted within the last ten years. A few are older food and drug regulations enacted in the 1940s.

Planned Policies

Every country reported policy that will be enacted, or areas for which policy will likely be developed. For specific details about each country, see Table 5-1. The majority of countries (8 of 12) reported plans for strengthening regulations to ensure rational use of antimicrobials. Common policy goals included development and implementation of manuals and national guidance documents for AMU. More than half of the countries (7 of 12) identified plans for improving AMR and AMU surveillance and monitoring. Some countries described activities to strengthen or establish policy or tools to address AMR. One country described plans to strengthen existing legislation. Another common theme of planned policy included efforts to improve multi-sectoral coordination. Five countries mentioned establishing or strengthening multi-sectoral collaboration to address AMR particularly for finalizing NAPs. Afghanistan reported drafting a NAP on AMR through multi-sectoral collaboration:

> "*The Ministry of Public Health and the Ministry of Agriculture (AMR) focal points are working to draft the AMR national action plan (NAP). The NAP will determine the national strategy for addressing AMR until 2020. AMR focal points participated in an AMR workshop in Morocco in March 2016. The NAP should be finalized by 2017 for implementation*." – Afghanistan

Myanmar reported similar plans:

> "*Planned AMR/AMU policies include monitoring and control of AMR/AMU strategy, Action Plan of National Veterinary drugs residues control program and chemicals in animal production based from the strategy needs to be developed (registration is in place but authorization, usage, prescription, labeling requirement and pre and post market surveillance need to be enforced), A manual of procedures needs to be developed*." – Myanmar

Table 5-1. Countries response to the question "what are planned national policies to address AMR and AMU in food and agriculture?"	
Country	**Planned policy**
Afghanistan	• Veterinary drug importation and regulation • Focal points from the Ministries of Public Health and Agriculture are drafting an AMR National Action Plan
Bangladesh	• Strategy on AMR Prevention • Establish a multi-sectoral approach for planning and coordination of activities related to AMR. • Promote and ensure rational use of antimicrobials • Promote and strengthen infection prevention and control measures • Review, update, and strengthen regulatory provisions • Institutionalize a surveillance system for AMR containment
Bhutan	• Draft NAP • Establish a governance structure to spearhead activities on AMR • Promote rational use of AMs at all levels of human and veterinary healthcare. • Institute surveillance and monitoring system of AMR & antimicrobial use.
Cambodia	• Reduce antimicrobial use in food-producing animals. • Inter-sectoral collaboration. • Create an enabling regulatory framework. • Establish surveillance and monitoring system. • Ensure prudent use of antimicrobials. • Inspect farms, slaughterhouses, processing facilities, laboratories, private research and academic institutions, veterinary drugs and vaccines, veterinary services, and feed product outlets. • Meat quality control including testing of drug residues and microbial contamination. • Encourage local production of veterinary medicines and vaccines. • Establish strong collaboration between MoH and MAFF. • Establish a strong regulatory framework for authorization and control of the quality of veterinary medicines. • Develop Essential Medicines List for the animal sector. • Conduct pre-licensing safety evaluation of antimicrobials for veterinary use; consider the potential for resistance to drugs used in human medicine. • Ban non-therapeutic use of antimicrobials (e.g. growth promoters). • Restrict the use of antimicrobials identified as critically important in human medicine in food-producing animals. • Require prescriptions for all antimicrobials used for disease control in food-producing animals. • Measure and monitor antibiotic residue in food products from animal sources. • Establish monitoring system for AMR in food-producing animals. • Implement the Codex Alimentarius and OIE guidelines related to antimicrobial resistance • Promote better animal husbandry and good farming practices
India	• Inter-Sectoral Coordination Committee on Antimicrobial Resistance • Technical Advisory Group on Antimicrobial Resistance • Core Working Group on Antimicrobial Resistance
Indonesia	• Develop national-level AMR-AMU Strategy • Implement integrated surveillance • Develop manual on the prudent use of antimicrobials • Define central and local government's responsibility in supervising production, supply, and distribution of veterinary drugs. • Limit access to antimicrobials • Veterinary drug restriction and certification

Respondents were asked to identify the main determinants of AMR and AMU policies in their respective countries. The most common response was the increasing concern for human health with nine out of twelve countries reporting this as the key determinant of AMR and AMU policy. More than one third of countries (4 out of 12) reported increasing international concern of AMR as another important driver of policy. Other responses included inter-sectoral collaboration and the socio-economic consequences of adverse trade outcomes as influencing AMR policy. The intensification and changing livestock production systems were mentioned by a few countries. Respondents also commonly discussed concern regarding the transfer of antibiotic residues and resistant bacteria from agriculture to the environment. Two countries mentioned concern for animal health as a key driver of AMR policy. Three countries described research or surveillance as determinants of AMR and AMU policy. For instance, a respondent from Indonesia described findings from monitoring activities of AMR in animal products that revealed a rising prevalence of AMR, particularly in poultry products, as a driver of AMR policy. A respondent from Samoa stated that the results of a 2016 country situational analysis on AMR was a key driver of AMR policy. The following two quotes demonstrate national determinants of AMR and AMU policy.

> "*Antimicrobials are critical in the management and treatment of infectious diseases… AMR has serious socioeconomic implications and is of global concern. There is a global drive toward combating AMR and Bhutan supports the international community*" – Bhutan

> "*Overuse and misuse of antimicrobials is acknowledged. (Drivers of AMR and AMU policy include) Increased multi-resistant organisms for commonly used antimicrobials; high treatment costs; low quality and inefficient drugs are prevalent in the local market; and need for available information on evidence-based risk due to AMR/AMU*" – Sri Lanka

Institutions for implementing policies and legislation

Government level entities were the most commonly identified institution primarily responsible for implementing AMR/AMU policy. Ministries of health, agriculture, or the economic sector were typically mentioned. Private entities were also frequently identified, primarily pharmaceutical companies, health care facilities, medical and veterinary practitioners, and farmers and livestock companies. Community and civil sector actors were also identified as crucial for implementing AMR and AMU policy in the food and agriculture sector. These include medical and veterinary associations, research institutions, and consumers.

Stakeholders

Respondents identified a range of key stakeholders critical in shaping AMR and AMU policies. The most commonly identified stakeholders included veterinary pharmaceutical associations, farmers' associations, animal processing plants, veterinary medical associations, economic and trade sectors and researchers and academics. Ministries of animal, agriculture, and human health ministries were picked by every respondent as important stakeholders. International organizations including FAO, the WHO and OIE were also identified. Representative from six counties reported livestock producers or farmers as stakeholders in shaping AMR and AMU policies. For more details, see Table 5-2. Respondents from Philippines describe key stakeholders as the following:

> "*Government Regulators including the Dept. of Health, Dept. of Agriculture, and Dept. of Interior and Local Government; law makers and budget allocators; manufacturers, distributers, importers, retailers (drug stores); animal producers; medical and veterinary practitioners; and international organizations*" – Philippines

Enforcement

Participants were asked to identify efforts to ensure compliance of AMR and AMU policy. The most common responses focused on monitoring and surveillance of AMR and AMU. Other common responses included inspection and regulation of antimicrobial agents, and ensuring registration of antimicrobials. Plans for ongoing efforts included implementing good veterinary and agricultural practices, awareness raising campaigns, capacity building and support from regulatory authorities. Viet Nam, India, and Indonesia described plans for strengthening enforcement of existing policies through enhancing law enforcement, and strict compliance with regulatory authorities on AMR and AMU policy See Table 5-2. for specific country responses.

Viet Nam describes processes for improving policy enforcement:

> *"(To ensure policy compliance) develop AMR awareness raising material, enhance AMR awareness for key stakeholders, strengthen inspection and monitoring of the production, trading and use of antibiotics and strict sanctioning for violations."* – Viet Nam

Table 5-2. Responses to the question "how will you ensure or improve compliance to AMR and AMU policy?"

Country	Efforts to improve enforcement and compliance
Bhutan	• Monitoring report of Drug Regulatory Authority Pharmaco-vigilance system on antibiotics • Bhutan Agriculture and Food Regulatory Authority reports on food monitoring
Cambodia	• Veterinary drugs shall be registered for specific uses, in accordance with their risks on human and animal health. • No person or legal entity will be allowed to trade veterinary drugs unless they have a license from the Department of Agriculture, to import, export, package, repackage, inventory, distribute and wholesale in the Kingdom of Cambodia. • Procedure and standard for registration had been defined by the proclamation of MAFF that regulate the purchase, prescription, and use of [hazardous] veterinary drugs in accordance with their risk.
India	• Regular data collection and information • Strengthen surveillance system for AMR • Massive awareness among stakeholders • Requisite capacity building • Strict compliance by regulatory authorities
Nepal	• Implementation of OIE PVS Gap Analysis and Recommendations • Approval of veterinary drug act and implementation • Good veterinary practices • Code of conduct for veterinarians and veterinary para-professionals on proper use of antibiotics
Philippines	• Monitoring and surveillance of AMR/AMU • Registration of antimicrobial agents • Inspection and licensing of establishments engaged in the production, importation, distribution, and sale of antimicrobial agents
Samoa	• The Ministry of Health, in collaboration with other government ministries, should raise awareness, and conduct programs and workshops. • The lack of funding to conduct further testing of meat and fish products. • People smuggling drugs across the border
Viet Nam	• Develop AMR awareness raising material • Enhance AMR awareness for key stakeholders

	• Strengthen inspection and monitoring of the production, trade, and use of antibiotics • Strict sanctions for violations

Constraints and Challenges for Policy Compliance

Seven of the twelve countries identified constraints to AMR policy compliance. The most important constraints, according to the respondents, was capacity: the lack of infrastructure, limited financial resources, insufficient laboratory capacity, and the lack of human resources including technical support and expertise. Low awareness of AMR among the general population, as well as key populations including veterinarians, was mentioned as an important constraint. A few countries mentioned inter-sectoral coordination and gaps in legal and regulatory controls as constraints or barriers to compliance of AMR policy. See Table 5-3. for more details.

Table 5-3. Constraints to AMR and AMU policy compliance

Country	**Constraints to compliance**
Bangladesh	• Lack of adequate manpower, lack of skills, lack of necessary logistics, financial constraints.
Bhutan	• Manpower shortage, skills and capacity, laboratory facilities, research capacity, limited awareness and knowledge of AMR
Cambodia	• Shortage of laboratories • Variation in methods (laboratory testing) • Lack of information: limited data in AMU and AMR in food producing animals • Limited inter-sectoral collaboration • Insufficient knowledge and training: lack of training on appropriate use of antimicrobials in food producing animals and insufficient understanding of their potential contributions to AMR in humans. • Perverse incentives: increasing sales profits by veterinarians and farms influence the inappropriate use of AMs • Gaps in legal and regulatory controls: insufficient legislation and regulations to restrict the availability and use of AMs in food-producing animals
Myanmar	• Infrastructure, human resources, laboratory capacity upgrading and testing • Low awareness • Need for contributions from citizens, ethicists, policy makers, practitioners and industry • Policy, advocacy, innovation and research, surveillance and funding, Post marketing of veterinary drugs
Samoa	• The lack of fund to conduct a further testing of meat and fish product • People smuggling drugs across the border
Sri Lanka	• Regular monitoring, targeted surveillance, failure to record treatment

Viet Nam	• Lack of awareness of AMR and AMU of farmers and consumer • Lack of financial resources

DISCUSSION

Recently, a range of policy recommendations have been proposed to combat AMR in humans and animals (WHO, 2015; Dar et al., 2016; Landers et al., 2012; FAO, 2016). In 2011, WHO's World Health Day was dedicated to AMR with the release of a policy package (WHO, 2011). This policy package outlines six priority areas where action is needed for countries to adequately address AMR. In 2015, the World Health Assembly, in coordination with the World Organization for Animal Health (OIE), and the Food and Agriculture Organization (FAO), adopted a Global Action Plan (GAP) on AMR. The GAP outlines specific recommendations for countries to prevent and decrease the spread of AMR. A key recommendation of the GAP is the development of country specific National Action Plans (NAPs). The GAP expects that all WHO Member States will develop their own NAPs in line with the global plan by May 2017 (GAP, 2015). To effectively strengthen national policy among countries in Asia, understanding regulatory activities and planned policy is essential.

This analysis demonstrates that across the twelve countries there are ongoing efforts to strengthen and adapt policy to address AMR and AMU. All respondents reported at least one national policy currently enacted or drafted to address AMR and AMU. Most national policy either directly or indirectly addressing AMR and AMU, has been enacted or updated in the last ten years. Countries report plans for developing new policy or strengthening existing policies. Most planned updates focus on addressing objectives outlined by the GAP. Plans to update policy frequently concentrate on rational use policies aimed at optimizing and promoting responsible antimicrobial use. Efforts to draft and implement NAPs were frequently described as planned policy actions.

Respondents described plans for improving multi-sectoral coordination. Most strategies include increasing coordination and establishing mechanisms to foster collaboration between human health and animal and agriculture sectors. Coordination between animal and agriculture ministries and ministries or departments related to the environment, trade or education, were not described. This is a critical gap as multi-sectoral coordination helps countries increase commitment, awareness and action from different sectors to ensure appropriate and effective AMR response (GAP, 2015; Nweneka et al., 2009). Improving infection prevention and control (IPC) efforts in animals and agriculture was not commonly identified as a policy priority by the responding countries. This is an important policy area to support, as IPC efforts in low and middle income countries are chronically underprioritized and underfunded (Dar et al., 2016). Building political consensuses and support for these initiatives is necessary to increase IPC capacity in the region and decrease the need for antimicrobials. Another key area that was not described is the need to increase regulation on sales and distribution of antimicrobials particularly veterinarians right to prescribe and sell antibiotics. As countries continue to strengthen policy economic incentives should be eliminated by decoupling veterinarians' right to both prescribe and sell antibiotics.

There is consensus among countries regarding the institutions key to implementing AMR and AMU policy with a focus on ministries of health and agriculture. Specific regulatory authorities within ministries were infrequently described as agencies critical to implementing AMR and AMU policy. Plans for improving compliance with AMR and AMU policy were highlighted by many respondents. Common responses included strategies for capacity building and strengthening implementation of existing policies. To more effectively address gaps in policy compliance, countries should conduct comprehensive assessments and compare implementation best practices with existing policy (Dar et al., 2016).

Consideration of stakeholder engagement in policy implementation is an important step countries should take to reduce AMR (Archawakulathep et al., 2014). Several respondents identified low awareness among stakeholders on AMR as a major constraint to AMR/AMU policy compliance. Stakeholder awareness raising was commonly identified as planned policy. Countries identified a variety of stakeholders important in shaping AMR and AMU policies. Mostly respondents focused on ministries of animal and human health and departments within these ministries. Engaging additional stakeholders would be beneficial, particularly stakeholders involved in implementing AMR and AMU policies.

Concern for human health was the main determinant for improving national AMR policy response identified by respondents. Only two countries mentioned concern for animal health as a driver of AMR policy. This likely reflects the economic concern of AMR on animal health (FAO, 2005). Few countries described surveillance, monitoring, or research as determinants or influencers of AMR or AMU national policies. This suggests that there is a need to increase surveillance and monitoring initiatives and support building laboratory and research capacity for AMR. Building this capacity is particularly important for establishing evidence-based policies. Currently there is a significant variation in the amount, and type of research on AMR and AMU from the countries included in this review (Archawakulathep et al., 2014). Respondents described planned activities to build the evidence base on AMR and AMU. However, research outside of surveillance and monitoring activities was not explicitly mentioned. WHO and FAO have described research priority areas for countries to build their evidence base with a priority on understanding AMU and the economic impact of AMR. Research on AMU is particularly important to ensure that policies are based on local context and consider the national drivers of antimicrobial use. Additionally, monitoring activities on drug quality will be beneficial for countries to adopt to curb the production of counterfeit and substandard antimicrobials.

CONCLUSION

Findings from this analysis can inform policy and future recommendations for AMR and AMU interventions. Critical gaps that should be addressed at a policy level include limited regulation on the use of antimicrobials in animals particularly nontherapeutic use, enhanced coordination between sectors, infection prevention and control efforts, low-awareness among key stakeholder groups and lack of evidence on AMR and AMU. To address the evidence gap, policy should support activities beyond surveillance and monitoring including research to better understand AMU and AMR in the national context. Policy-makers should consider infection prevention and control initiatives when adapting AMR policy and their great potential for reducing the need for antimicrobials. National investments in improved animal husbandry practices and disease prevention measures have demonstrated effective at reducing AMU in various settings (Dar et al., 2016). Although data regarding the enforcement is sparse, the effectiveness of existing policy is likely weakened as a result of insufficient enforcement capacity, infrastructure, and funding. Building this capacity is needed to address key constraints and challenges including lack of adequate infrastructure and resources such as technical support and expertise.

As AMR continues to receive increased attention and political commitment, countries should ensure that appropriate and context specific policies are implemented. Countries often prioritize actions described in the GAP, however policy-makers should consider local context and national needs when adapting and prioritizing these recommendations into policy. Before full implementation of policy countries should consider piloting new polices on a small-scale to ensure that new policies are appropriate and meet the needs of the local context. Integrating findings from this analysis to inform recommendations made from international organizations, government and non-governmental organizations will produce more effective AMR policy responses to protect public health from this growing threat. Findings from this analysis can also support the resources allocation process and ensure sufficient funds and resources are appropriated to create a more enabling policy environment for AMR response.

Chapter 6:

Conclusions

OVERALL CONCLUSIONS

The intensification of animal production and changes in agricultural practices present favorable conditions for the emergence and spread of old and new diseases. Policies to promote national animal production should consider potential unintentional disease outcomes such as AMR and brucellosis. Consideration of disease prevention and control in developing policies to promote animal production is crucial for safeguarding public health. Overall the purpose of this research was to characterize and describe national policies to promote animal production and the impact and potential consequences of these national policies. Studies in this dissertation provide information on the re-emergence of a zoonotic disease and countries current and proposed policy framework to manage and protect public health from AMR.

The first and second analysis in this dissertation focused on understanding the impact of national policy decisions and a disease re-emergence event in Thailand. This was considered through a cross-sectional study in Thailand examining small-scale goat farmers' knowledge, attitudes and practices associated with brucellosis and through estimating seroprevalence using national brucellosis surveillance data. The first analysis supported previous findings that brucellosis poses an occupational risk as farmers engaged in high risk behaviors including minimal use of personal protective equipment and limited actions when purchasing a new animal. This study determined that farmers have knowledge of brucellosis in goats; however, understanding of the disease in humans and other animals is limited. Additional important findings include that participants perceived that their risk of infection was low with the majority reporting that they or a member of their household, were not at risk for brucellosis.

This analysis helps to identify specific human risk exposure to the disease through animal husbandry practices and further highlights the occupational risk of goat farming. Additionally, this study identifies areas where knowledge of brucellosis could be strengthened through farmer education and training. Future research should consider examining human seroprevalence of brucellosis among farmers to understand how animal husbandry factors influence seroprevalence in humans. Additional focus should be on areas where little or no research has been conducted such as the eastern region of Thailand. This research can be used to inform national policy and consideration of increased farmer training and education on disease prevention and transmission specific to brucellosis and other diseases of concern.

Results from the second analysis estimating brucellosis seroprevalence using the national brucellosis surveillance system data indicate that certain regions of Thailand have higher seroprevalence of brucellosis at both the animal and herd level. During the three-year period, 2013 had the highest proportion of herds that tested positive for brucellosis at 13.80% (372/2,695). Provinces in the eastern and western regions of Thailand had the highest proportion of animals and herds testing positive during all three years. Contrary to previous research indicating the southern provinces as an area of brucellosis concern, this research found the southern region to have the lowest herd and animal seroprevalence. Findings from this analysis indicate that additional control measures would be beneficial to reduce the prevalence of brucellosis in small ruminants in Thailand with efforts concentrated in areas with higher prevalence. It is recommended that policy be strengthened to increase DLD testing throughout the country to provide a more thorough representation of brucellosis throughout the country. From 2013 – 2015 27.3% of the total small ruminant population and 7.79% of the total small ruminant herd population were tested and included in the national surveillance system. As goat farming continues to increase, potential human health consequences should be taken into consideration when adapting animal husbandry policy and policies to control brucellosis to ensure appropriate initiatives are implemented to control brucellosis.

Results from analysis of AMR and AMU policy in food and agriculture provides a deeper understanding of Southeast Asian countries' current regulatory framework and capacity to respond to AMR. Analysis revealed countries have existing policies that can be used to address

AMR at the national level. With the development of NAPs to address AMR, many countries have the foundation to develop AMR/AMU awareness initiatives, to provide support for surveillance and monitoring systems, and improve infection prevention and control systems. Despite a plethora of existing policies, several limitations exist. Policies suffer from weak standards for limiting or reducing the use of critically important and nontherapeutic use of antimicrobials. Most countries do not have legislation that specifically reduce or restrict the use of antimicrobials for use as growth promoters or for disease prevention. Although data regarding the enforcement is sparse, the effectiveness of existing policy is likely diluted as a result of insufficient enforcement capacity, infrastructure, and funding. Countries in Southeast Asia have established policy to address and control the spread of infectious diseases; however, the extent to which these have been fully implemented is not yet understood. Future studies on effectiveness of these policies would be beneficial.

The final part of this dissertation was to understand countries awareness of their policy to address AMR and AMU, implementation of these policies and national goals for improving AMR response. Focus group discussions with key informants on AMR policy provided further insight and information on national policies, including background information about national strategies, local constraints and challenges, and proposed AMR policy. Results from this analysis suggest that some countries have limited awareness of national policies already enacted that directly or indirectly address AMR. Countries described plans for enacting new policies with a focus on developing and implementing national action plans. Proposed policies address objectives described in the World Health Organization Global Action Plan to address AMR particularly around awareness raising and building surveillance and monitoring capacity. Overall common policy gaps among the countries interviewed included a gap in ongoing efforts to regulate the use of antimicrobials, limited coordination between sectors, weak policy support for building awareness and limitations in efforts to build the evidence base for AMR and AMU. Additional limitations included limited policy response for improving infection prevention and control efforts. Key stakeholders in shaping AMR and AMU policies focused on veterinary pharmaceutical associations, farmers' associations and ministries of agriculture. Common gaps and constraints described by countries to address AMR include limitations in infrastructure and capacities and lack of financial and human resources. Additionally, low awareness among key stakeholder groups and the general population was identified as an important challenge in addressing AMR.

Diseases that are transmissible either directly or indirectly between animals and humans, such as AMR and brucellosis, pose significant threats to global animal and human health. This research serves as a reminder that food production systems are dynamic and integrated to human health. As countries continue to adapt policy to increase food production, consideration of the spread and growth of disease need to be considered. Additionally, further work is needed to integrate across human and animal sectors. This was especially evident from the initial interviews and review of AMR policies across countries. Further dialog is needed. Overall, this research can be used to inform future evaluation and studies on the impact of agriculture policies and infectious diseases in low resource settings, strengthen new policy, inform training and education initiatives and provide greater awareness and understanding of factors influencing emergence and re-emergence of infectious diseases.

BIBLIOGRAPHY

Food and Agriculture Organization. (2008). Livestock and human and animal health. Retrieved from: http://www.fao.org/docrep/012/i0680e/i0680e05.pdf Accessed on April 20, 2017.

Wolfe N.D., Claire Panosian Dunavan2 & Jared Diamond. Origins of major human infectious diseases. Nature 447, 279-283 (17 May 2007) | doi:10.1038/nature05775

Graham, J. P., Leibler, J. H. et al. (2008) The animal human interface and infectious disease in industrial food animal production: rethinking biosecurity and biocontainment. Public Health Rep, 123(3): 282-299.

Gray, G. C., Trampel, D. W. et al. (2007) Pandemic influenza planning: shouldn't swine and poultry workers be included? Vaccine, 25(22): 4376-4381.

Otte, J., Roland-Holst, D. et al. (2007) Industrial livestock production and global health risks. Food and Agriculture Organization of the United Nations, Pro-Poor Livestock Policy Initiative Research Report.

Slingenbergh M.,de Balogh, K., Wint, W. Ecological sources of zoonotic diseases. Rev. sci. tech. Off. int. Epiz., 2004, 23 (2), 467-484

Morse, S. S. (2001). Factors in the emergence of infectious diseases. Plagues and politics (pp. 8-26) Springer.

Keesing F., Belden L., Daszak P., Dobson A., Harvell C.D., Holt R., Hudson P., Jolles A., Jones K., Mitchell C., Myers S., Bogich T., Ostfeld R. Impacts of biodiversity on the emergence and transmission of infectious diseases. Nature. 2010; 468:647–652. doi: 10.1038/nature09575.

Greger, M. (2007). The human/animal interface: emergence and resurgence of zoonotic infectious diseases. Critical Reviews in Microbiology, 33(4), 243-299.

Fresco L. O. (2009). Challenges for food system adaptation today and tomorrow. Environ. Sci. Policy 12, 378–385. doi:10.1016/j.envsci.2008.11.001

Jones K. E., Patel N. G., Levy M. A., Storeygard A., Balk D., Gittleman J. L., Daszak P. 2008Global trends in emerging infectious diseases. Nature 451, 990–993 doi:10.1038/nature06536

Perry B., Grace D. 2009. The impacts of livestock diseases and their control on growth and development processes that are pro-poor. Phil. Trans. R. Soc. B 364, 2643–2655 (doi:10.1098/rstb.2009.0097)

Weiss R. A., McMichael A. J. 2004. Social and environmental risk factors in the emergence of infectious diseases. Nat. Med. 10, S70–S76 (doi:10.1038/nm1150)

Tomley FM, Shirley MW. (2009). Livestock infectious diseases and zoonoses.Philos Trans R Soc Lond B Biol Sci. 2009 Sep 27; 364(1530): 2637–2642. doi: 10.1098/rstb.2009.0133

Food and Agriculture Organization. (2015). Major perspective issues and possible policy response. Retrieved from http://www.fao.org/docrep/005/y4252e/y4252e07a.htm. Accessed on April 15, 2017.

Brooks J. (2010). Agricultural Policy Choices in Developing Countries: A Synthesis. Retrieved from https://www.oecd.org/tad/agricultural-policies/46340461.pdf. Accessed on April 15, 2017.

Thornton PK, Livestock production: recent trends, future prospects. Philos Trans R Soc Lond B Biol Sci. 2010 Sep 27; 365(1554): 2853–2867. doi: 10.1098/rstb.2010.0134

World Bank. (2017). East Asia Pacific. Retrieved from http://www.worldbank.org/en/region/eap/overview. Accessed on April 20, 2017.

Food and Agriculture Organization (2017). The rise of unregulated livestock production in East and Southeast Asia prompts health concerns. Retrieved from http://www.fao.org/asiapacific/news/detail-events/en/c/469630/. Accessed April 10, 2017.

Millar J, Photakoun V. Livestock development and poverty alleviation: revolution or evolution for upland livelihoods in Lao pdr. International journal of agricultural sustainabilit. doi:10.3763/ijas.2007.0335

Delgado C., Rosegrant, M., Steinfi eld, H., Ehui, S. and Courbois, C. (1999) Livestock to 2020. The Next Food Revolution. Food, Agriculture and the Environment Discussion Paper 28. Washington: International Food Policy Research Institute.

Theungphachan T. (2008) National Agriculture and Forestry Research Institute. Livestock & Fisheries Products Quality Assurance Unit NAHC, DLF http://lad.nafri.org.la/fulltext/3783-0.pdf

Dean, A. S., Crup, L., Greter, H., Schelling, E., & Zinsstag, J. (2012). Global burden of human brucellosis: A systematic review of disease frequency. PLoS Neglected Tropical Diseases. 6(10), e1865.

Bamaiyi, P.H., Hassan, L., Khairani-Bejo, L., et al. (2014) Updates on Brucellosis in Malaysia and Southeast Asia. Malaysian Journal of Veterinary Research, 5, 71-82.

Chiewchanyont B, Appassakij H, Silpapojakul K. Brucellosis as an emerging disease in thailand: A report of three cases with Review of literatures (โรค บ รู เซล โล ซิ ส ใน ประเทศไทย). *Journal of Health Science-วารสาร วิชาการ สาธารณสุข*. 2011;18(5):643-649.

Nakavisut, S., & Anothaisinthawee, S. (2014). Country report-thailand. Asian-Australasian Dairy Goat Network,95.

World Health Organization. (2012). http://apps.who.int/iris/bitstream/10665/44812/1/9789241503181_eng.pdf

Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States. 2013. Retrieved from https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed April 17, 2017.

Ventola, C. L. (2015). The Antibiotic Resistance Crisis: Part 1: Causes and Threats. Pharmacy and Therapeutics, 40(4), 277–283.

World Bank Group. Drug Resistant Infections: A Threat to Our Economic Future. The World Bank 2016. Retrieved from http://pubdocs.worldbank.org/en/689381474641399486/1701381-AMR-Lab-Report-Web.pdf. Accessed October 8, 2016.

Landers TF, Cohen B, Wittum TE, Larson EL. A review of antibiotic use in food animals: perspective, policy, and potential. Public Health Reports. 2012. Jan-Feb;127 (1):4-22. 10.1177/003335491212700103

Richter CH, Custer B, Steele JA, Wilcox B, Xu J. (2015). Intensified food production and correlated risks to human health in the Greater Mekong Subregion: a systematic review Environmental Health. 14:43. DOI: 10.1186/s12940-015-0033-8.

Nhung NT, Cuong NV, Thwaites G, Carrique-Mas J. (2016). Antimicrobial Usage and Antimicrobial Resistance in Animal Production in Southeast Asia: A Review. Anbitoics (Basel). Dec; 5(4): 37. doi: 10.3390/antibiotics5040037

Van Boeckela TP, Browerb C, Gilbert M, Bryan T, Grenfell BT, Levina SA, Robinsoni TP, Teillanta A, Laxminarayan R., Global trends in antimicrobial use in food animals. PNAS. 2015. 112 (18), 5649–5654.

World Health Organization. (2010). Growing threat from counterfeit medicines. Retrieved from http://www.who.int/bulletin/volumes/88/4/10-020410/en/Accessed on April 20, 2017.

Devendra C. Investments on pro-poor development projects on goats: Ensuring success for improved livelihoods. Asian-Australasian journal of animal sciences. 2013;26(1):1.

Anothaisinthawee S, Nakavisut S, Yuyuen S, Thongchumroon T. Dairy goats in thailand: Potential opportunities and challenges. 2012:58-61.

Laosiritaworn, Y., Hinjoy, S., Chuxnum, T., Vagus, A., & Choomkasien, B. P. (2007). Re-emerging human brucellosis, thailand 2003. Bulletin of the Department of Medical Services, 32(4), 415.

Seleem, M. N., Boyle, S. M., & Sriranganathan, N. (2010). Brucellosis: A re-emerging zoonosis. Veterinary Microbiology, 140(3), 392-398.

Corbel, M. J. (2006). Brucellosis in humans and animals World Health Organization, Food and Agriculture Organization of the United Nations, World Organization for Animal Health.

Srinoy, B., C. Chantalakhama, S. Saithanoo, and K. Pattamarakha. 1999. The adoption of recommended practices by dairy farmers in southern Thailand. Asian-Aust. J.Anim. Sci. 12(7) : 1116 – 1122.

Roth F, Zinsstag J, Orkhon D, Chimed-Ochir G, Hutton G, Cosivi O, Carrin G, Otte J. Human health benefits from livestock vaccination for brucellosis: case study. Bulletin of the World Health Organ.2003;81:867–876

Rotes-Qurol J. Osteo-articular sites of brucellosis. Ann Rheum Dis. 1957;16(1):63-68.

Madkour MM. Madkour’s brucellosis. Springer Science & Business Media; 2001.

World Organisation for Animal Health. (2012). Bovine brucellosis OIE terrestrial manual. World Organization for Animal Health, Paris, France; 615-650.

Gunes Y, Tuncer M, Guntekin U, et al. Clinical characteristics and outcome of brucella endocarditis. Trop Doct. 2009;39(2):85-88. doi: 10.1258/td.2008.070436 [doi].

Blasco J. A review of the use of B. melitensis rev 1 vaccine in adult sheep and goats. Prev Vet Med. 1997;31(3):275-283.

Plumb, G. E., Olsen, S. C., & Buttke, D. (2013). Brucellosis: 'one health' challenges and opportunities. Revue Scientifique Et Technique (International Office of Epizootics), 32(1), 271-278.

Ruben B, Wong P, Band JD, Colville J. Person-to-person transmission of Brucella melitensis. Lancet.1991;337:14–5.

Molavi M, Sajjadi H, Nejatizade A. Effective methods for appropriate diagnosis of brucellosis in humans and animals (review article). Online Journal of Animal and Feed Research (OJAFR). 2014;4(3):60-66.

Spink WW. The nature of brucellosis. U of Minnesota Press; 1956.

Yousefi-Nooraie R, Mortaz-Hejri S, Mehrani M, Sadeghipour P. Antibiotics for treating human brucellosis. Cochrane Database Syst Rev. 2012;10.

Bordier, M., & Roger, F. (2013). Zoonoses in south-east asia: A regional burden, a global threat. Animal Health Research Reviews.14(01), 40-67

Strategic and Operational Guidance on Animal and Environmental Aspects: National Action Plans on Antimicrobial Resistance for Developing Countries, 2017, Centre for Science and Environment, New Delhi. Retrieved from http://www.cseindia.org/userfiles/strategic-and-operational-guidance-NAP-on-AMR-for-Developing-Countries.pdf. Accessed on April 5, 2017.

Mølbak K, Baggesen DL, Aarestrup FM, Ebbesen JM, Engberg J, Frydendahl K, Gerner-Smidt P, Petersen AM, Wegener HC. (1999). An outbreak of multidrug-resistant, quinolone-resistant Salmonella enterica serotype typhimurium DT104. N Engl J Med. Nov 4; 341(19):1420-5.

Loeffen VA, Bakker J, Klassen C, Wulf M. (2005). Methicillin-resistant Staphylococcus aureus in pig farming. Emerg Infect Dis. 11(12):1965-6.

Food and Agriculture Organization. (2016). The FAO Action Plan on Antimicrobial Resistance (2016 – 2020). Retrieved from http://www.fao.org/3/a-i5996e.pdf. Accessed October 10, 2016.

Gelband, H., Delahoy, M. Policies to Address Antibiotic Resistance in Low- and Middle-Income Countries: National and International Action on Antimicrobial Resistance. The Center for Disease Dynamics, Economics, and Policy. July 2014. Retrieved from https://www.cddep.org/sites/default/files/abrinlmics_cddep_gelband_and_delahoy_9-14.pdf. Accessed on April 17, 2017.

O'Neill J. (2016). "Tackling drug-resistant infections globally: final report and recommendations," in Review on Antimicrobial Resistance, ed. O'Neill J., editor. (London: Review on Antimicrobial Resistance).

Leder K, Torresi J, Libman MD, et al. (2013). GeoSentinel surveillance of illness in returned travelers, 2007–2011. Ann Intern Med. 2013;158:456–468.

Ekpanyaskul C1, Santiwattanakul S, Tantisiriwat W, Buppanharun W. (2012). Factors associated with seropositive antibodies to Brucella melitensis in the Nakhon Nayok, Thailand. J Med Assoc Thai. Dec; 95 Suppl 12:S40-6.

Marshall BM, Levy SB. (2011). Food Animals and Antimicrobials: Impacts on Human Health. Clin Microbiol Rev. Oct; 24(4): 718–733.

Addis, M. (2015). Public health and economic importance of brucellosis: A review. Public Health, 5(7)

Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health Thailand (2003). Weekly Epidemiol Surv Rep. 34, 495-8.

Danprachankul, S., Chiewchanyont, B., Appassakij, H., Silpapojakul, K. (2009). Brucellosis as an Emerging Disease in Thailand: A Report of Three Cases with Review of Literatures. Journal of Health Science. 18(5), 643-648.

Excel (2015). (Part of Microsoft Office Professional Edition) [computer program]. Microsoft, 2015.

Godfroid, J., Scholz, H., Barbier, T., Nicolas, C., Wattiau, P., Fretin, D., . . . Moriyon, I. (2011). Brucellosis at the animal/ecosystem/human interface at the beginning of the 21st century. Preventive Veterinary Medicine, 102(2), 118-131.

Holt, H. R., Eltholth, M. M., Hegazy, Y. M., El-Tras, W. F., Tayel, A. A., & Guitian, J. (2011). Brucella spp. infection in large ruminants in an endemic area of egypt: Cross-sectional study investigating seroprevalence, risk factors and livestock owner's knowledge, attitudes and practices (KAPs). BMC Public Health, 11, 341-2458-11-341. doi:10.1186/1471-2458-11-341 [doi]

Inchaisri C, Prasomsri P, Boonserm T, Hogeveen H, Ajariyakajorn K. (2016). A stochastic simulation model for brucellosis eradication in goat flocks in an area with high flock prevalence but low animal prevalence. Small Rumin Res, ;136:227-37

Kanitpun R. (2014). Thailand Country Report, The 4th FAO-APHCA/OIE/DLD Regional Workshop on Brucellosis Diagnosis and Control in Asia-Pacific Region Proficiency Test and Ways Forward, Chiang Mai, Thailand. March 2014

Laosiritaworn, Y., Hinjoy, S., Chuxnum, T., Vagus, A., & Choomkasien, B. P. (2007). Re-emerging human brucellosis, thailand 2003. Bulletin of the Department of Medical Services, 32(4), 415.

Lindahl, E., Sattorov, N., Boqvist, S., & Magnusson, U. (2015). A study of knowledge, attitudes and practices relating to brucellosis among small-scale dairy farmers in an urban and peri-urban area of tajikistan. PloS One, 10(2), e0117318. doi:10.1371/journal.pone.0117318.

Molavi, M., Sajjadi, H., & Nejatizade, A. (2014). Effective methods for appropriate diagnosis of brucellosis in humans and animals (review article). Online Journal of Animal and Feed Research (OJAFR), 4(3), 60-66.

Montiel, D. O., Frankena, K., Udo, H., Baer, N. M. K., & van der Zijpp, A. (2013). Prevalence and risk factors for brucellosis in goats in areas of mexico with and without brucellosis control campaign. Tropical Animal Health and Production, 45(6), 1383-1389.

Paitoonpong, L., Ekgatat, M., Nunthapisud, P., Tantawichien, T., & Suankratay, C. (2006). Brucellosis: The first case of king chulalongkorn memorial hospital and review of the literature. J Med Assoc Thai, 89(8), 1313-1317.

Perry, B. D. (2002). Investing in animal health research to alleviate poverty ILRI (aka ILCA and ILRAD).

Sergeant, E., & Perkins, N. (2015). Epidemiology for field veterinarians: An introduction CABI.

Spink, W. W. (1956). The nature of brucellosis U of Minnesota Press.

StataCorp. (2015). Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Wongphruksasoong, V., Santayakorn, S., Sitthi, W., Chuxnum, T., Pipatjaturong, N., Kunthu, A., . . . Doung-ngern, P. (2016). An outbreak of brucella melitensis among goat farmers in thailand, december 2009. OSIR Journal, 5(1), 14-21.

Te-chaniyom, T., Sinanan, N., Watthanakul, M., Choomkasean, P., Chuxnum, T., Smithsuwan, P., Pimprapai, W, Hinjoy, S. An Investigation of Human Brucellosis and Goat Farm Network Analysis in Ratchaburi Province, 2013. Outbreak, Survelliance and Investigation Reports. (2015). Vol 8, issue 2, p. 7 – 12.

Canadian Food Inspection Agency. 2013. Recommended Best Practices. Retrieved from: http://www.inspection.gc.ca/animals/terrestrial-animals/biosecurity/standards-and-principles/producer-guide-goats/eng/1375213342187/1375213659306?chap=2#s8c2. Accessed June 13, 2017.

Centers for Disease Control and Prevention. (2017). Brucellosis. Retrieved from https://www.cdc.gov/brucellosis. Accessed on April 19, 2017.

Laosiritaworn, Y., Hinjoy, S., Chuxnum, T., Vagus, A., & Choomkasien, B. P. (2007). Re-emerging human brucellosis, thailand 2003. Bulletin of the Department of Medical Services, 32(4), 415.

Kaewket W. Seroepidemiological studies of Brucella melitensis antibodies in goats and contacted goat farmers at Kanchanaburi Province [Thesis]. Bangkok: Faculty of Graduate Studies, Mahidol University. 2008.

Satchaphun B. The situation of goat production, consumption and marketing in southern region of Thailand. (2014). Retrieved from http://region9.dld.go.th/Section/education/pdf /ed-goat/ed-goat2.pdf.

Sagarasaeranee O, Kaewkalong S, Sujit K, Chanachai K. Seroprevalence of brucellosis in small ruminants in Thailand, 2013. OSIR. 2016 9(4):7-10. Retrieved from http://www.osirjournal.net/issue.php?id=105.

QGIS Geographic Information System Development Team. Open source geospatial foundation project. http://www.qgis.org/en/site/forusers/index.ht ml. Accessed April 24, 2017.

StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Sujit K, Wongphruksasoong V. The situation of animal diseases outbreak in Thailand between 2005 and 2012: the data from the World Animal Health Information System (WAHIS). 2014 Jan 24. Retrieved from http://dcontrol.dld.go.th/index.php/km/reseas e/2554-24-1-2014WAHIS.html. Accessed April 10, 2017.

Bamaiyi, P.H., Hassan, L., Khairani-Bejo, S., Zainal Abidin, M., Ramlan, M., Adzhar, A., Abdullah, N., Hamidah, N.H.M., Norsuhanna, M.M. and Hashim, S.N. 2015. The prevalence and distribution of Brucella melitensis in goats in Malaysia from 2000-2009. Prev. Vet. Med. 119(3-4):232-236

Ninprom, T., Nonthasorn, P., Thiptara A., Kongkaew, W., Prevalence and spatial distribution of brucellosis in goats in the southernmost provinces of Thailand in 2014. Volume 11 Number 2 (Sep-Dec 2016) : 16-26. Thai-NIAH eJournal. http://niah.dld.go.th/th/files/ejournal/v11n2t01.pdf

McFadden, D. "Conditional logit analysis of qualitative choice behavior." Frontiers in Econometrics. Academic Press.1974. Pp. 105-142.

World Health Organization. (2015). Antimicrobial resistance: a priority for global health action. Retrieved from http://www.who.int/bulletin/volumes/93/7/15-158998/en/. Accessed September 20, 2016.

World Health Organization. (2016). Global Action Plan on Antimicrobial Resistance. Retrieved from http://www.who.int/antimicrobial-resistance/global-action-plan/en/. Accessed May 10, 2017.

Food and Agriculture Organization. (2016). The FAO Action Plan on Antimicrobial Resistance (2016 – 2020). Retrieved from http://www.fao.org/3/a-i5996e.pdf. Accessed October 10, 2016.

Dar OA, Hasan R, Schlundt J, et al. Exploring the evidence base for national and regional policy interventions to combat resistance. The Lancet. 2016;387:285–95.http://www.sciencedirect.com/science/article/pii/S0140673615005206.

Årdal C, Outterson K, Hoffman SJ, et al. International cooperation to improve access to and sustain effectiveness of antimicrobials. Lancet (2015) published online Nov 18. http://dx.doi.org.ezp1.lib.umn.edu/10.1016/S0140-6736(15)00470-5

Organisation for Economic Co-operation and Development. (2016). Antimicrobial Resistance Policy Insights. Retrieved from https://www.oecd.org/health/health-systems/AMR-Policy-Insights-November2016.pdf. Accessed December 12, 2016.

Hershberger E, Oprea1 SF, Donabedian SM, Perri M, Bozigar P, Bartlett P, Zervos MJ. (2005). Epidemiology of antimicrobial resistance in enterococci of animal origin. Journal of Antimicrobial Chemotherapy. 55, 127–130. doi:10.1093/jac/dkh508

Speksnijder DC, Mevius DJ, Bruschke CJM, Wagenaar JA. (2015). Reduction of Veterinary Antimicrobial Use in the Netherlands. The Dutch Success Model. Zoonoses and Public Health. 62, 79–87.doi: 10.1111/zph.12167

Organisation for Economic Co-operation and Development. (2016). Global Antimicrobial Use in the Livestock Sector. Retrieved fromhttp://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=TAD/CA/APM/WP(2014)34/FINAL&docLanguage=En. Accessed October 5, 2016.

Food and Agriculture Organization. (2016). Drivers, dynamics and epidemiology of antimicrobial resistance in animal production. Retrieved from http://www.fao.org/3/a-i6209e.pdf. Accessed April 17, 2017.

World Organisation for Animal Health. (2010). Terrestrial Animal Health Code, 2010. Retrieved from http://web.oie.int/eng/normes/mcode/a_summry.htm. Accessed November 6, 2016.

Food and Agriculture Organization. FAOLEX Database. Retrieved from http://www.fao.org/faolex/en/. Accessed October 8, 2016.

World Health Organization. (2017). FAO/OIE/WHO Tripartite Collaboration on AMR. Retrieved from http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/tripartite/en/. Accessed April 28, 2017.

Nweneka CV, Tapha-Sosseh NT, Sosa A. Curbing the menace of antimicrobial resistance in developing countries. Harm Reduction Journal. 2009: 6:31. DOI: 10.1186/1477-7517-6-31

World Health Organization. (2017). Critically important antimicrobials for human medicine 5th Revision. Retrieved from http://www.who.int/foodsafety/publications/antimicrobials-fifth/en/. Accessed on April 17, 2017.

Archawakulathep A, Kim C, Meunsene D, Handijatno D, Hassim HA, Rovira H., … Chuanchuen R. Perspectives on antimicrobial Resistance in livestock and livestock products in asean countries. The Thai J of Vet Med. 2014: 44(1): 5-13. Retrieved from http://www.tci-thaijo.org/index.php/tjvm/article/view/17308/15635.

Agersø Y, et al. DANMAP 2011: Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Foods and Humans in Denmark. Copenhagen, Denmark: The Danish Integrated Antimicrobial Resistance Monitoring and Research Program. 2011. Available: http://goo.gl/XoxPPm

van den Bogaard AE, et al. The effect of banning avoparcin on VRE carriage in the Netherlands. J Antimicrob Chemother 46(1):146–148 (2000); http://dx.doi.org/10.1093/jac/46.1.146.

Agersø Y, Aarestrup FM. Voluntary ban on cephalosporin use in Danish pig production has effectively reduced extended-spectrum cephalosporinase-producing Escherichia coli in slaughter pigs. J Antimicrob Chemother 68(3):569–572 (2013); http://dx.doi.org/10.1093/jac/dks427.

Decree of the Head of National Agency of Drug and Food Control Republic of Indonesia on Criteria and Procedure of Drug Registration. No. HK.00.05.3.1950. Jakarta, 2003.

Nga DT, Kim NG, Hoa NP, Hoa NQ, Nguyen TT, Loan TH, Toan TK, Phuc HD, Horby P, Yen VY, Kinh NV, Wertheim HF. Antibiotic sales in rural and urban pharmacies in northern Vietnam: an observational study. BMC Pharmacol Toxicol, 2014; 15:6.

Asia News Network. Banned agricultural substances rampant in Vietnam. Retrieved from http://asianews.network/content/banned-agricultural-substances-rampant-vietnam-14367. Accessed April 15, 2017.

Asia News Networks. Antibiotics use alarming - Indonesian health minister. Retrieved from http://www.asianews.network/content/antibiotics-use-alarming-indonesian-health-minister-18720. Accessed April 15, 2017.

Pincock S. WHO tries to tackle problem of counterfeit medicines in Asia. BMJ. 2003 Nov 15; 327(7424): 1126.

Phys.org. Banned antibiotics in Asian fish imports: Australia. Retrieved from https://phys.org/news/2012-05-antibiotics-asian-fish-imports-australia.html#jCp. Accessed April 15, 2017.

Food and Agriculture Organization. Antimicrobial Resistance What is it. Retrieved from http://www.fao.org/antimicrobial-resistance/background/what-is-it/en/. Accessed April 15, 2017.

Gale J, Mulvany L, Reel M. How Antibiotic-Tainted Seafood From China Ends Up on Your Table. Bloomberg Businessweek. Retrieved from https://www.bloomberg.com/news/features/2016-12-15/how-antibiotic-tainted-seafood-from-china-ends-up-on-your-table. Accessed April 15, 2017.

Huttner B, Goossens HF, Verheij TF, Harbarth S, CHAMP Consortium. 2010. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. Lancet Infect Dis. 10, 17–31 (doi:10.1016/S1473-3099(09)70305-6)

Filippini M, Ortiz LG, Masiero G. 2013. Assessing the impact of national antibiotic campaigns in Europe. Eur. J. Health Econ. 14, 587–599.

Agersø Y, Aarestrup FM. Voluntary ban on cephalosporin use in Danish pig production has effectively reduced extended-spectrum cephalosporinase-producing Escherichia coli in slaughter pigs. J Antimicrob Chemother 68(3):569–572 (2013).

Japan Ministry of Forestry and Fisheries. Assessment guideline for the Effect of Food on Human Health Regarding AntimicrobialResistant Bacteria Selected by Antimicrobial Use in Food producing animals. 2004. Retrieved from http://www.fsc.go.jp/senmon/hisiryou/taiseikin_hyoukasisin_english.pdf. Accessed May 10, 2017.

Leslie, T. et al., 2009. Epidemic of Plasmodium falciparum malaria involving substandard antimalarial drugs, Pakistan, 2003. Emerging Infectious Diseases, 15(11), pp.1753– 1759.

World Health Organization. Antimicrobial resistance: a priority for global health action. Retrieved from http://www.who.int/bulletin/volumes/93/7/15-158998/en/. Accessed September 20, 2016.

Food and Agriculture Organization. The FAO Action Plan on Antimicrobial Resistance (2016 – 2020). Retrieved from http://www.fao.org/3/a-i5996e.pdf. Accessed October 10, 2016.

Organisation for Economic Co-operation and Development. Antimicrobial Resistance Policy Insights. Retrieved from https://www.oecd.org/health/health-systems/AMR-Policy-Insights-November2016.pdf. Accessed December 12, 2016.

European Centre for Disease Prevention and Control. Antimicrobial Resistance and Healthcare-associated Infections. 2017. Retrieved from: http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial-resistance-healthcare-associated-infections-programme/Pages/ARHAI.aspx. Accessed on April 17, 2017.

WHO, Tuberculosis Factsheet, Online. Retrieved from: http://www.who.int/mediacentre/ factsheets/fs104/en/. Accessed on April 12, 2017.

Gelband, H., Delahoy, M. Policies to Address Antibiotic Resistance in Low- and Middle-Income Countries: National and International Action on Antimicrobial Resistance. The Center for Disease Dynamics, Economics, and Policy. 2014. Retrieved from https://www.cddep.org/sites/default/files/abrinlmics_cddep_gelband_and_delahoy_9-14.pdf. Accessed on April 17, 2017.

Archawakulathep A, Kim C, Meunsene D, Handijatno D, Hassim HA, Rovira H., … Chuanchuen R. Perspectives on antimicrobial Resistance in livestock and livestock products in asean countries. The Thai J of Vet Med. 2014: 44(1): 5-13. Retrieved from http://www.tci-thaijo.org/index.php/tjvm/article/view/17308/15635.

Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States. 2013. Retrieved from https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed April 17, 2017.

Hershberger E, Oprea1 SF, Donabedian SM, Perri M, Bozigar P, Bartlett P, Zervos MJ. Epidemiology of antimicrobial resistance in enterococci of animal origin. Journal of Antimicrobial Chemotherapy. 2005: 55, 127–130. doi:10.1093/jac/dkh508

Speksnijder DC, Mevius DJ, Bruschke CJM, Wagenaar JA. Reduction of Veterinary Antimicrobial Use in the Netherlands. The Dutch Success Model. Zoonoses and Public Health. 2015: 62, 79–87.doi: 10.1111/zph.12167

Marshall, B. M., & Levy, S. B. (2011). Food Animals and Antimicrobials: Impacts on Human Health. Clinical Microbiology Reviews, 24(4), 718–733. http://doi.org/10.1128/CMR.00002-11

Mendelson M., Matsoso M. (2015). The South African antimicrobial resistance strategy framework. *AMR Control* 54–61.

World Health Organisation, Global Action Plan on Antimicrobial Resistance, WHO, 2015. Retrieved from http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/. Accessed on January 10, 2017.

World Health Organization. The WHO policy package to combat antimicrobial resistance. 2011. Retrieved from http://www.who.int/bulletin/volumes/89/5/11-088435/en/. Accessed on January 10, 2017.

Food and Agriculture Organization. Chapter 2 Trends in Animal Health: problems and challenges. Retrieved from http://www.fao.org/docrep/005/Y3542E/y3542e05.htm. Accessed on June 16, 20

APPENDIX 1.

Table 6. Key policy documents reviewed addressing antimicrobial resistance and use in animals and agriculture

Country	Title and Year
Cambodia	○ Cambodia National Policy to Combat AMR (2014) ○ Law on Animal Health and Production (2016) ○ The law on the amendment of law on management of Pharmaceuticals (1996 updated 2007) ○ National Strategy to Combat Antimicrobial Resistance (2015 – 2017) (2014) ○ National Action Plan to address AMR in agriculture, fisheries, food and livestock (2016 – 2020) (2016) ○ Prakas No. 225 (MAFF) on technical standards for constructing slaughterhouses ○ Sub-Decree 16 on the Sanitary Inspection of Animal and Animal Products (2003) ○ Sub-Decree No. 26 ANKr-BK on the Creation and Management of Village Animal Health Agents, (2001) ○ Joint Prakas No. 363 (MAFF MOH) on management of production, import, export and trade of veterinary drugs ○ Sub-Decree No. 14/ANK on the inspection of animal sanitary and animal originated products ○ Prakas on Roles and Responsibilities of Control Agent for Pharmaceutics, Food, Medical equipment, and Cosmetics and Private Medical, Paramedical and Medical Aid Services ○ Sub-decree on agricultural standard and materials No. 69 (1998) ○ Sub-Decree No.17 ANKr-BK on the Organization and Functioning of the Ministry of Agriculture, Forestry and Fisheries (2000) ○ Sub-decree No.108 on the Management of Slaughterhouse and the Control of Hygiene (2007)
Indonesia	○ Law No. 18/2009 on Husbandry and Animal Health. ○ Government Regulations no. 78, 1992 - veterinary drugs control ○ Decree of MoA no. 15, 1994 - veterinary drugs inspector ○ Decree of Moa No. 806, 1994 - the veterinary drugs classification ○ Decree of MoA no. 15, 2008 - monitoring of residue and microbial contamination in animal products ○ Government regulation no. 95, 2012 - the veterinary public health aspects ○ Ordinance no.432 and 435, 1912 ○ Government Regulation no. 15, 1977 ○ Government Regulation no. 78, 1992 control of veterinary drugs ○ Decree of MoA no. 15, 1994 the veterinary Drugs Inspector ○ National Action Plan on AMR in Indonesia (2017 – 2019) ○ Food and Medicine Supervisory Board (Badan Pengawas Obat dan Makanan) regulation No. HK.00.05.3.02706 of 2002 on Medicine Promotions ○ Decree of MOH No 189/Menkes/SK/III/2006 on National Medicine Policy ○ Kebijakan Obat Nasional (National Medicine Policy), 2007 Ministry of Health, Jakarta ○ Decree of the Minister of Oceanic and Fisheries no. 26, 2002 ○ no. 4158, 2003 the veterinary drugs used in aquaculture. ○ Consumer Protection Law no. 8, 1999, article no.19 responsibilities of the producers to protect consumers from deviations of their products ○ Decree of MoA no. 806, 1994 the veterinary drugs classifications ○ Food Law no. 7, 1996, article no.20 and 21 food quality assurance and laboratory testing for food ○ Government regulation no.22, 1983 the Veterinary Public Health aspect ○ Decree of MOA no. 426, 1994 establishment and operations of the Quality Control Laboratory for Livestock Products
Lao PDR	○ Law on Drugs and Medical Products (2011) ○ Law on Livestock Production and Veterinary Matters (2008) ○ Law on Agriculture (1998) ○ Law on Health Care (2005) ○ Revised National Medicine Policy (2003) ○ National Food Safety Policy (2009) ○ Ministerial Decision on Management Animal Clinics and Veterinary Products Shop ○ Ministerial Decision on the Basic Principle for the Application of Sanitary and Phytosanitary Measures in Plant and Animal Product Administration, No. 0039/MAF (2012) ○ Roles, Tasks and Responsibility of the Department of Agriculture and Agriculture Extension (1992) ○ List of Essential Medicines Of Lao, Guidelines On Drugs ○ Decree on the Prevention and Control of Animal Diseases (2012) ○ Technical Norms on Livestock and Livestock Product Management (2000) ○ Ministerial Decision on the Organization and Operation of Sanitary and Phytosanitary Enquiry Point (2011) ○ Regulation on Food Registration (1994) ○ Regulation Governing Drug Registration No. 1441/MOH ○ Prime Minister’s Decree on Livestock Management PM (1993) ○ Regulation on Livestock Management (1997)

Myanmar	○ Animal Health and Development Law (17/93) ○ Animal Husbandry and Health Law under amendment to better cover veterinary drugs ○ Livestock Development Law (1999) ○ National Food Law (1997) ○ Environmental Protection Law ○ Union of Myanmar National Drug Law (1992)
Viet Nam	○ Law on Veterinary Medicine (2015) ○ Law on Food Safety (2010) ○ Circular No. 10/2016/TT-BNNPTNT "Issuing the list of approved and prohibited veterinary drugs" (2016) ○ (Ministry of Health, National Action Plan on Combatting Drug Resistance, (2013-2020) (2013) ○ Drug Law 105/2016/QH13 ○ Pharmaceutical Law (2005) ○ Animal Health Law (2015) ○ Circular No. 13/2016 / TT-BNN dated 02/6/2016 Management of Veterinary Drug ○ Veterinary Ordinance 18/2004/PL-UBTVQH11 promulgated on 29 April 2004 by National Assembly of The Socialist Republic of Vietnam. ○ Decision No 03 /2009/TT-BNN regulating "Labeling of Veterinary Products" (2009) ○ Inter-Ministerial Circular No. 16/2013/TTLT-BYT-BNN&PTNT (2013) ○ Circular 39/2013/ TT-BYT Regulations on management of medicines for human use on non-commercial imports and exports ○ Government Decree 33/2005/ND-CP dated 15 March 2005 stipulating implementation of a numbers of articles of the Veterinary Ordinance 18/2004/PL-UBTVQH11. ○ National Action Plan On Combatting Drug Resistance (2013 – 2020) ○ Viet Nam Integrated One Health Action Strategic Plan for the period (2016-2020) ○ Decision No 51/2009/TT-BNNPTNT "Veterinary Hygiene Conditions for Veterinary Drug Production and Trading Enterprises" (2009) ○ Decision No 10/2006/QD-BNN regulating "Procedures for Production, Registration, Import and Circulation of Veterinary Drugs, Materials for Veterinary Drug Production, Biological Products (pro-biotics), Micro-organisms and Chemicals" (2006)